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-PySO2CF2H) enables C(sp2)−C(sp2) bond formation through selective C(sp2)−S bond cleavage, which demonstrates the new reactivity of 2-PySO2CF2H 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.

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 catalysis (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 As of 2018, we reported the first iron-catalyzed difluoromethylation of arylzincs with difluoromethyl 2-pyridyl sulfone (2-PySO2CF2H) via selective C(sp3)−S bond cleavage (Scheme 1a).7a The Baran group developed a nickel-catalyzed cross-coupling between aryl zinc reagents and alkyl heteroaryl sulfones to form C(sp3)−C(sp3) 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-PySO2CF2H to forge C(sp2)−C(sp2) bonds via selective C(sp2)−S bond cleavage, which was different from our previous work (Scheme 1b).

Our study commenced with the nickel-catalyzed reductive cross-coupling of 4-iodotoluene (1a) with 2-PySO2CF2H (2a). Initially, when we employed 10 mol % of NiCl2, 10 mol % of 4,4′-di-tert-butyl-2,2′-bipyridine (dtbbpy), 2.0 equiv of zinc...
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 variation of the amounts of zinc powder proved to have an influence on the reaction efficiency (Table 1, entries 4–16). It was found that the monodentate phosphine ligand triphenylphosphane (PPh₃) 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 NiCl₂, 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(sp³)–C(sp³) coupling product, namely, Ar–CF₂H was detected, which is in sharp contrast with our previous report on the iron-catalyzed cross-coupling reaction between arylzincs and 2-PySO₂CF₂H.2

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-PySO₂CF₂H (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 (3l and 3m), trifluoromethyl (3k and 3l), ketone (3n–o), ester (3p), sulfone (3q), and trifluoromethoxy (3r) groups) reacted with 2-PySO₂CF₂H. 
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-PySO₂CF₂H. 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-PySO₂CF₂H, 2-(methylsulfonyl)pyridine (2-PySO₂CH₃) 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-PySO₂CF₂H (2a) and fluoroalkyl 2-pyridyl sulfones (2b, 2-PySO₂CF₂H) 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-PySO₂CF₃) and methyl 2-pyridyl sulfone (2d, 2-PySO₂CH₃) provided only a trace amount of 3d under the standard reaction conditions.

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-PySO₂CF₂H 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 was observed as a byproduct via ¹⁹F NMR in 82% yield under the standard reaction conditions, which suggests that the generation of a difluoromethyl radical from 2-PySO₂CF₂H (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 NiCl₂(dppe)₅ to Ni(0) species A by Zn(0). The oxidative addition of 2-PySO₂CF₂H to Ni(0) species A affords an arylnickel(II) species B. The subsequent transmetalation of the arylnickel(II) species B with the arylzinc reagent, which is in situ generated from aryl iodides and Zn(0), 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.
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), the present work not only provides a new strategy for the formation of biaryl but also gives new insights into the new reactivity of fluoroalkyl sulfones. Compared with results previously reported by us and others, 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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**REFERENCES**


(5) For selected examples, see: (a) Wu, J.-C.; Gong, L.-B.; Xia, Y.; Song, R.-J.; Xie, Y.-X.; Li, J.-H. Nickel-Catalyzed Kumada Reaction of Tosylalkanes with Grignard Reagents to Produce Alkenes and Alkynes. J. Am. Chem. Soc. 2018, 140, 53


(13) For a discussion of another possible pathway when manganese(0) was used as the reductant, see the Supporting Information.