

Switching from 2-pyridination to difluoromethylation: ligand-enabled nickel-catalyzed reductive difluoromethylation of aryl iodides with difluoromethyl 2-pyridyl sulfone

Wei Du, Qinyu Luo, Zhiqiang Wei, Xiu Wang, Chuanfa Ni & Jinbo Hu*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

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The divergent reductive cross-coupling with an ambident electrophile is rare. Previously, we demonstrated a nickel-catalyzed reductive 2-pyridination of aryl iodides with difluoromethyl 2-pyridyl sulfone (2-PySO₂CF₂H) *via* selective C(sp²)-S bond cleavage of the sulfone by using a phosphine ligand. In this communication, we report a novel nickel-catalyzed reductive coupling of aryl iodides and 2-PySO₂CF₂H reagent, which constitutes a new method for aromatic difluoromethylation. The use of a tridentate terpyridine ligand is pivotal for the selective C(sp³)-S bond cleavage of the sulfone. This method employs readily available nickel catalyst and 2-PySO₂CF₂H as the difluoromethylation reagent, providing a facile access to difluoromethylarenes under mild reaction conditions without pre-generation of arylmetal reagents.

nickel catalysis, difluoromethylation, 2-PySO₂CF₂H, reductive cross-coupling

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Cross-electrophile coupling reaction has been developed as an effective strategy for the formation of C-C bonds [1]. The metal-catalyzed coupling of two carbon electrophiles instead of the conventional metal-catalyzed coupling between a carbon electrophile and a carbon nucleophile can avoid the limitations of preformed carbon nucleophiles such as limited availability, strong basicity, and problematic transmetalation [2]. In the past decade, an arsenal of carbon electrophiles including common organic halides and pseudohalides and derivatives of ketones, alcohols, amines, and carboxylic acids have been exploited as coupling partners under reductive conditions [1,3]. Sulfones as the chemical chameleons have been widely used in organic synthesis [4], and their coupling with carbon nucleophiles under either metal-catalyzed or metal-free conditions has witnessed numerous

advances [5]. However, to the best of our knowledge, the transition-metal-catalyzed direct reductive cross-coupling of sulfones with carbon electrophiles has been still underdeveloped [6,7].

On the other hand, difluoromethylation is of great synthetic interest because the difluoromethyl group has been used as a bioisostere of hydroxyl group or thiol group and can act as a weak hydrogen bond donor with varying lipophilicity [8]. Aromatic difluoromethylation has been a key approach for installing a CF₂H group into organic molecules [9]. Considering the easy availability and low cost of the aryl and CF₂H sources, reductive cross-coupling between aryl halides and a proper difluoromethyl electrophile is an ideal method to obtain difluoromethyl arenes. Recently, Zhang's group [10] and MacMillan's group [11] have developed nickel or palladium-catalyzed reductive cross-coupling between chloro-/bromodifluoromethane and aryl (pseudo)ha-

*Corresponding author (email: jinbohu@sioc.ac.cn)

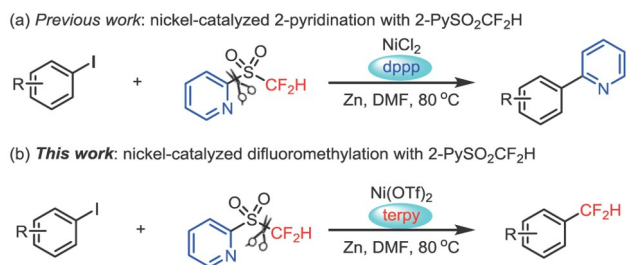
lides. However, the requirement of gaseous ozone-depleting substances XCF_2H ($\text{X} = \text{Cl}, \text{Br}$) may impede the broad application of this method. Therefore, the development of a new reductive aromatic difluoromethylation method that employs operationally simple CF_2H electrophiles is necessary.

Fluoroalkyl sulfones are bench-stable and easily accessible and have been widely used as versatile fluoroalkylation reagents [5,12]. In 2018, we realized an iron-catalyzed aromatic difluoromethylation between diarylzinc reagents and difluoromethyl 2-pyridyl sulfone (2-PySO₂CF₂H) [13]. Meanwhile, Baran and coworkers [14] reported a nickel-catalyzed aromatic fluoroalkylation between aryl zinc reagents and fluoroalkyl heteroaryl sulfones. These seminal results suggest the feasibility of using difluoromethyl heteroaryl sulfones as CF_2H electrophiles. However, one major challenge to the development of a method for reductive difluoromethylation of aryl halides with sulfones was to achieve efficient $\text{C}(\text{sp}^3)\text{-S}$ bond cleavage of difluoromethyl heteroaryl sulfones. Indeed, our initial attempt on nickel-catalyzed reductive cross-coupling between aryl iodides and 2-PySO₂CF₂H readily afforded the 2-pyridination products instead of the expected difluoromethylation products, proceeding through the $\text{C}(\text{sp}^2)\text{-S}$ bond cleavage of the sulfone reagent (Scheme 1a) [6]. We envisioned that the reductive aromatic difluoromethylation may be tamed by identifying a proper catalyst system to facilitate the $\text{C}(\text{sp}^3)\text{-S}$ bond cleavage of 2-PySO₂CF₂H. Herein, we report our success in a nickel-catalyzed reductive cross-coupling between aryl iodides and 2-PySO₂CF₂H to form $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^3)$ bonds via selective $\text{C}(\text{sp}^3)\text{-S}$ bond cleavage (Scheme 1b). This reductive difluoromethylation with 2-PySO₂CF₂H, in combination with our previously reported reductive 2-pyridination with 2-PySO₂CF₂H, constitutes a rare case of divergent reductive coupling of sulfones involving selective C-S bond cleavage.

Our investigation started with the nickel-catalyzed cross-coupling of iodobenzene (**1a**) with 2-PySO₂CF₂H using zinc as the reductant (Table 1). Previously, a combination of NiCl₂ and dppp afforded 2-phenylpyridine as the only cross-coupling product [6]. To achieve aromatic difluoromethylation, we initially investigated bidentate pyridine-type ligands (**L1-L4**) as these have been demonstrated to be effective for nickel-catalyzed aryl-alkyl cross-electrophile coupling reactions between aryl halides and alkyl halides [15]. The reaction was performed by employing 10 mol% of NiCl₂, 10 mol% of ligand and 2.0 equiv. of zinc powder in *N,N*-dimethylformamide (DMF) at 80 °C for 16 h. When 2,2'-bipyridine (**L1**) was used, the desired difluoromethylation product **2a** was formed in trace amounts (~1% yield) (Table 1, entry 1). Further improvement of the yield of **2a** was observed when using other bidentate nitrogen ligands **L2-L4** (Table 1, entries 2-4). These preliminary results suggested

the feasibility of aromatic difluoromethylation using nitrogen ligands. In these cases, the much lower yield of the difluoromethylation product **2a** than the conversion of 2-PySO₂CF₂H indicates that the competitive $\text{C}(\text{sp}^2)\text{-S}$ bond cleavage of 2-PySO₂CF₂H was dominant, which is supported by the detection of 2-phenylpyridine as the major coupling product (Table 1, entries 1 and 2). Next, we further screened other pyridine-type ligands aiming at improving the difluoromethylation. Higher conversions of 2-PySO₂CF₂H and increased yield of difluoromethylation product **2a** were detected when changing bidentate pyridine-type ligands **L1-L4** to tridentate terpyridine ligands **L5** and **L6** (Table 1, entries 5 and 6) [15b,16]. When Ni(acac)₂ was used instead of NiCl₂, terpyridine (**L5**) afforded **2a** in much higher yield (68%) than 4,4',4''-tris(*tert*-butyl)-2,2':6',2''-terpyridine (**L6**) (Table 1, entries 7 and 8). It is apparent that in addition to the correct choice of nitrogen ligand, nickel sources can play a pivotal role in this reductive $\text{Ar-CF}_2\text{H}$ coupling reaction. Thus, by using commercially available **L5** as the optimal ligand, several other nickel sources were investigated. The results showed that except for NiF₂ (Table 1, entry 9), all the tested nickel sources afforded the difluoromethylation product **2a** in improved yields (Table 1, entries 10-14). Ni(OTf)₂ was found to be the best source, giving the highest yield of **2a** (Table 1, entry 14). The low efficiency of NiF₂ probably results from the counterion effect of the fluoride ion, which may influence the reactivity of the nickel catalyst towards 2-PySO₂CF₂H. Subsequently, the loading of the catalyst was screened by using Ni(OTf)₂ as the optimal metal source and **L5** as the optimal ligand. Upon decreasing the catalyst loading to 5 mol% and keeping the metal-to-ligand ratio as 1:1, the yield slightly increased to 80% (Table 1, entry 15), whereas it decreased to some extent upon changing the metal to ligand ratio to 1:1.1 (Table 1, entry 16). In the former case, the side product 2-phenylpyridine was detected in only 7% yield. Finally, we screened the amount of aryl iodide required for the efficient utilization of 2-PySO₂CF₂H as the difluoromethylation source. As shown, increasing the amount of **1a** possessed little effect on the yield of **2a** (Table 1, entry 17), but a further decrease in the amount of **1a** was detrimental to the desired reaction (Table 1, entries 18 and 19). Based on all these results, the optimized reaction conditions were established as follows: aryl iodide and 2-PySO₂CF₂H in a molar ratio of 1:1.5 at 80 °C for 16 h in DMF using 5 mol% of Ni(OTf)₂/**L5** (1:1) in the presence of zinc powder (Table 1, entry 15). Note that the use of PhSO₂CF₂H instead of 2-PySO₂CF₂H failed to provide the $\text{Ar-CF}_2\text{H}$ coupling product (Table 1, entry 20), which is in line with the lower reduction potential of PhSO₂CF₂H (-2.05 V vs. Ag/AgCl) than 2-PySO₂CF₂H (-1.80 V vs. Ag/AgCl) [12d].

With the optimized reaction conditions in hand (Table 1, entry 15), we investigated the scope of nickel-catalyzed reductive cross-coupling of aryl halides with 2-PySO₂CF₂H



Scheme 1 Nickel-catalyzed divergent reductive cross-coupling with 2-PySO₂CF₂H via selective C–S bond cleavage. dppp = 1,3-bis-(diphenylphosphino)propane; terpy = 2,2′,6′,2′′-terpyridine (color online).

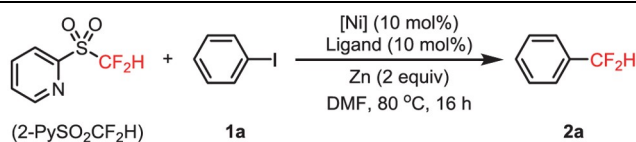
(Scheme 2). A wide range of aryl iodides, including iodo-biphenyls (**1j** and **1k**), iodonaphthalenes (**1n** and **1o**), iodo-fluorenes (**1l** and **1m**), iododibenzothiophene (**1t**) and iodicarbazole (**1u** and **1v**), were difluoromethylated in moderate to good yields. Various aryl substituents were amenable to the reaction, with electron-rich groups generally providing higher yields than electron-deficient groups. Iodobenzenes bearing electron-donating groups such as methyl (**1b** and **1c**), methoxy (**1e**, **1p** and **1p**), methylthio (**1f**), phenoxy (**1g**), acetal (**1s**), and diphenylamino (**1w**) could deliver the difluoromethylation products in 54%–82% yields. Iodobenzenes with the electron-withdrawing groups such as trifluoromethyl (**1h**) and acetyl (**1i**) groups afforded the corresponding difluoromethylation products in 45%–50% yields. Although iodobenzene with a simple *ortho*-substituent gave an inferior yield (**2d**), reactions of iodoarenes with a fused ring at the *ortho*-position gave moderate yields (**2n** and **2t**). Medicinally relevant complex aryl iodides including the empagliflozin intermediate (**1x**), derivative of chloramphenicol intermediate (**1y**), and anagliflozin intermediate (**1z**) were competent in this coupling reaction, as demonstrated by the formation of the corresponding difluoromethylation products in 46%–65% yields. However, the reaction system was incompatible with the phenolic hydroxyl group, as indicated by the failed difluoromethylation of 4-iodophenol (**1aa**). In addition to aryl iodides, some aryl bromides were also applicable to the reductive cross-coupling. When the aryl bromides were substituted with electron-withdrawing groups such as aldehyde group (**1ab**) and ester group (**1ac**) on the *para*-position, the difluoromethylation products were formed in 36%–42% yields.

To gain mechanistic insights into this nickel-catalyzed reductive cross-coupling reaction, we conducted several preliminary mechanistic experiments (Scheme 3). Firstly, to determine which electrophile was reduced initially, the reduction of PhI and 2-PySO₂CF₂H by zinc in the absence or in the presence of the catalyst was investigated. Consistency with the previous report [6], PhI could readily react with zinc to form PhZnI, which was confirmed by proton nuclear

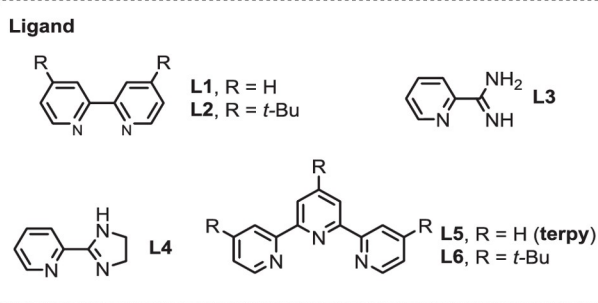
magnetic resonance (¹H NMR) analysis of the extracting solution in Et₂O after quenching with water (Scheme 3a). In the presence of the Ni(OTf)₂/terpy, PhI was reduced by zinc much faster, indicating that nickel can promote the reduction of PhI with zinc, probably *via* oxidative addition of ArI into the low-valent nickel species. Besides, the lack of homo-coupling product 1,1′-biphenyl in this transformation is in agreement with the detection of only a trace amount of 1,1′-biphenyl in the cross-coupling reaction between PhI and 2-PySO₂CF₂H. These results suggest that under the catalysis of Ni(OTf)₂/terpy, the formation of an Ar₂Ni species is disfavored. Unlike PhI, in the absence of a nickel catalyst, 2-PySO₂CF₂H was inert towards zinc (Scheme 3b). However, 2-PySO₂CF₂H could be reduced by zinc under the catalysis of Ni(OTf)₂/terpy (75% conversion in 16 h), albeit slower than the reduction of PhI. ¹⁹F NMR analysis of the reaction mixture showed that CF₂H₂ was formed in substantial amount; however, no difluoromethylzinc species [17] was detected. The use of deuterated DMF as the solvent led to the observation of CF₂HD (δ –144.0 ppm, dt, J = 50.0, 7.7 Hz) [17], indicating that the reduction of 2-PySO₂CF₂H by the low valent nickel species produced difluoromethyl radical rather than difluoromethyl anion. Secondly, to probe the possibility of arylzinc as an intermediate to participate in the cross-coupling reaction, we performed nickel-catalyzed cross-coupling of 2-PySO₂CF₂H with preformed phenylzinc iodide (Scheme 3c). In this case, a full consumption of 2-PySO₂CF₂H gave the product PhCF₂H only a 22% yield. This result suggests that the pre-generation of arylzinc followed by transmetalation with low valent nickel species may be a competitive pathway for the difluoromethylation; however, it should be less efficient than the direct oxidative addition of ArI to Ni(0).

Based on our experimental results and literature precedent [15a], we propose a plausible mechanism for the present nickel-catalyzed cross-electrophile coupling reaction, which involves the generation of a difluoromethyl radical and the reductive elimination reaction of a Ni(III) intermediate (Scheme 4). Initially, aryl iodides undergo oxidative addition to Ni(0) species **A** that is formed through the reduction of Ni(OTf)₂ species by Zn(0). Meanwhile, a difluoromethyl radical is generated through the single electron reduction of 2-PySO₂CF₂H by the Zn(0)/Ni(OTf)₂/terpy system. Subsequently, the arylnickel(II) species **B** reacts with the initially formed difluoromethyl radical to afford the Ni(III) intermediate **C**.

Reductive elimination of the cross-coupling product from species **C** generates a Ni(I) species **D**. The single electron transfer between the Ni(I) species **D** and 2-PySO₂CF₂H leads to 2-pyridylsulfinate-ligated Ni(II) species **E** and a difluoromethyl radical. The thus-generated difluoromethyl radical would come into the catalytic cycle. Finally, the Ni(II) species **E** is reduced by zinc to regenerate Ni(0) species

Table 1 Initial experiments and optimization^{a)}

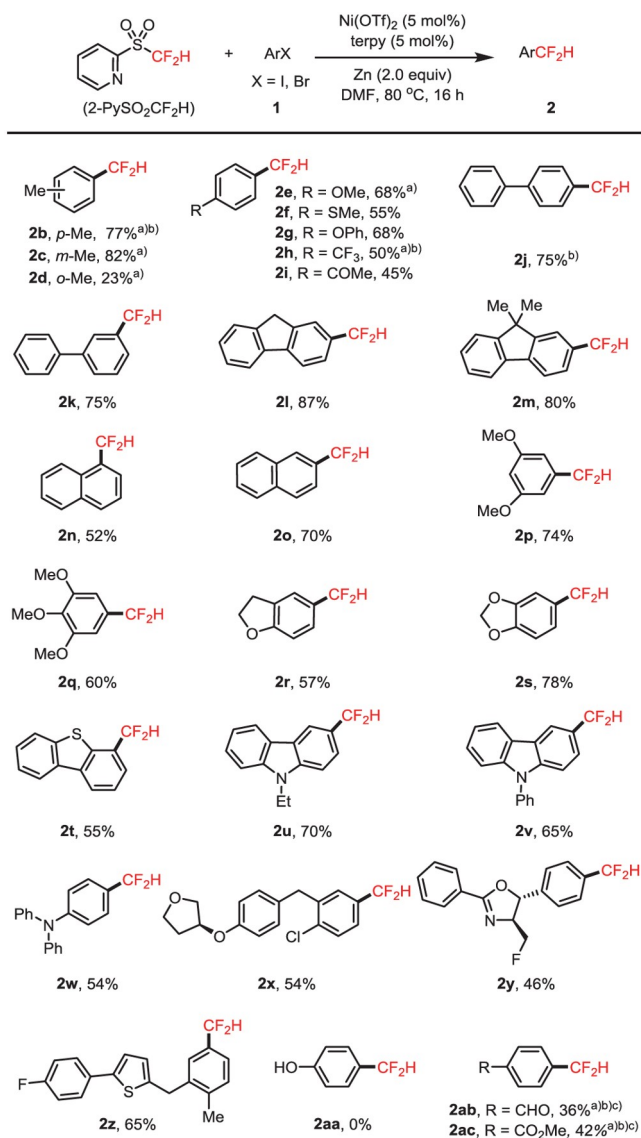
Entry	[Ni]	Ligand	1a /2-PySO ₂ CF ₂ H	2-PySO ₂ CF ₂ H, Conv. (%) ^{b)}	2a , Yield (%) ^{b)}
1 ^{c)}	NiCl ₂	L1	1:1.5	73	~1 (39) ^{d)}
2	NiCl ₂	L2	1.5:1	59	4 (35) ^{d)}
3	NiCl ₂	L3	1.5:1	53	8
4	NiCl ₂	L4	1.5:1	51	12
5	NiCl ₂	L5	1.5:1	94	51
6	NiCl ₂	L6	1.5:1	>99	54
7	Ni(acac) ₂	L5	1.5:1	>99	68
8	Ni(acac) ₂	L6	1.5:1	79	24
9	NiF ₂	L5	1.5:1	80	2
10	Ni(COD) ₂	L5	1.5:1	>99	56
11	NiCl ₂ (dme)	L5	1.5:1	>99	62
12	NiBr ₂ (dme)	L5	1.5:1	>99	56
13	NiI ₂	L5	1.5:1	>99	53
14	Ni(OTf) ₂	L5	1.5:1	95	78
15 ^{e)}	Ni(OTf) ₂	L5	1.5:1	>99	80 (7) ^{d)}
16 ^{f)}	Ni(OTf) ₂	L5	1.5:1	>99	75
17 ^{e)}	Ni(OTf) ₂	L5	1.7:1	>99	80
18 ^{e)}	Ni(OTf) ₂	L5	1.2:1	>99	69
19 ^{e)}	Ni(OTf) ₂	L5	1.1:1	>99	59
20 ^{g)}	NiCl ₂	L5	1.5:1	38	0



a) Reaction conditions: 2-PySO₂CF₂H (0.2 mmol, 1.0 equiv.), **1a** (0.3 mmol, 1.5 equiv.), [Ni] (10 mol%), ligand (10 mol%), zinc powder (1.0 mmol, 2.0 equiv.), DMF (0.16 M), 80 °C, 16 h. b) Performed with 2-PySO₂CF₂H (0.6 mmol, 1.5 equiv.) and **1a** (0.4 mmol, 1.0 equiv.). c) Conversion of 2-PySO₂CF₂H and yield of **2a** were determined by ¹⁹F NMR spectroscopy analysis of the reaction mixture using an internal standard. d) The number in the parentheses refers to the yield of 2-phenylpyridine determined by ¹H NMR spectroscopy analysis of the crude product after extraction with Et₂O. e) [Ni] (5 mol%), ligand (5 mol%). f) [Ni] (5 mol%), ligand (5.5 mol%). g) PhSO₂CF₂H (0.2 mmol, 1.0 equiv.) was used.

A. However, considering that arylzinc reagent can be formed even in the absence of the nickel catalyst, the transformation of the Ni(II) species **E** to the Ni(II) species **B** may also proceed through transmetalation of **E** with the arylzinc reagent that is *in situ* generated from aryl iodides and Zn(0) (for details, see [Supporting Information online](#)).

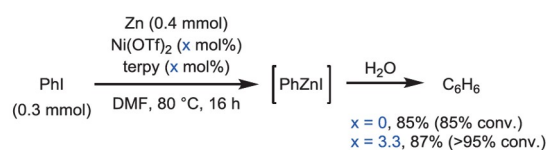
In summary, we have developed a novel nickel-catalyzed reductive cross-coupling reaction of 2-PySO₂CF₂H with aryl halides to forge C(sp²)-C(sp³) bonds *via* selective C(sp³)-S bond cleavage. When using 2,2':6',2''-terpyridine (**terpy**) as the ligand, nickel-catalyzed reductive difluoromethylation of aryl halides with 2-PySO₂CF₂H *via* the selective cleavage of



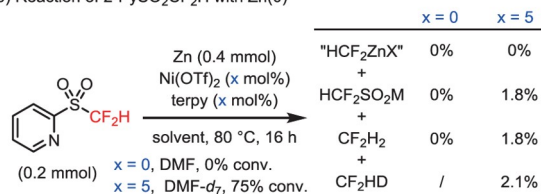
Scheme 2 Scope of Ni-catalyzed reductive cross-coupling of aryl halides with 2-PySO₂CF₂H. Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), ArX (0.45 mmol, 1.5 equiv.), Ni(OTf)₂ (0.015 mmol, 5 mol%), terpy (0.015 mmol, 5 mol%), zinc powder (0.6 mmol, 2.0 equiv.), DMF (0.16 M), 80 °C, 16 h, X = I. a) Yield was determined by ¹⁹F NMR spectroscopy analysis of the reaction mixture using PhOCF₃ the internal standard. b) Reaction was performed on 0.2-mmol scale. c) X = Br (color online).

the C(sp³)-S bond under mild reaction conditions was realized. This method provides facile access to difluoromethylarenes under mild reaction conditions without pre-generation of arylmetal reagents. This research is complementary with our previously reported nickel-catalyzed reductive 2-pyridination of aryl iodides with 2-PySO₂CF₂H via selective C(sp²)-S bond cleavage of the sulfone by using a phosphine ligand dppp [6]. In this respect, the role of the ligand is important, which can control the bond cleavage manner of the ambident electrophile 2-PySO₂CF₂H by tuning the reactivity of the nickel catalyst, thus facilitating divergent cross-coupling reactions. It is probably that the low

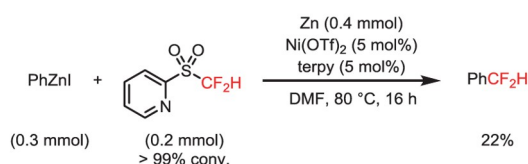
(a) Reaction of PhI with Zn(0)



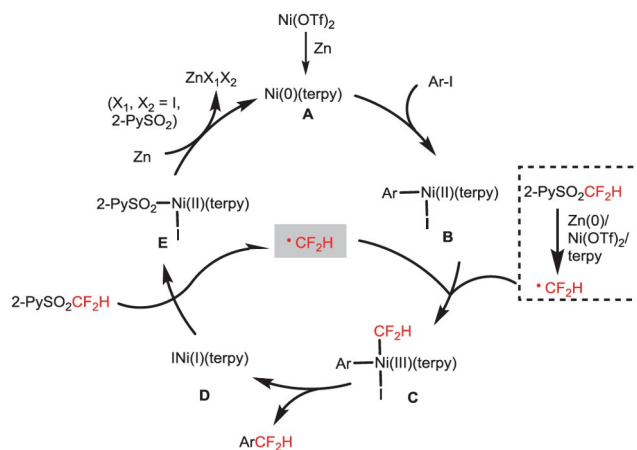
(b) Reaction of 2-PySO₂CF₂H with Zn(0)



(c) Reaction of 2-PySO₂CF₂H with pre-generated PhZnI



Scheme 3 Mechanistic Studies. Yield was determined by ¹H or ¹⁹F NMR spectroscopy analysis of the reaction mixture (color online).



Scheme 4 Proposed mechanism (color online).

valent nickel bound to dppp prefers oxidative addition to the C(sp²)-S bond due to the strong coordination ability of the electron-rich phosphine ligand, whereas the low valent nickel bound to terpyridine favors a single electron transfer process involving C(sp³)-S bond cleavage due to the steric hindrance and the reduced character of the terpyridine ligand [16].

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Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at <http://chem.scichina.com> and <http://link.springer.com/journal/11426>. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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