Direct Difluoromethylation of Aryl Halides via Base Metal Catalysis at Room Temperature

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S *Supporting Information*

ABSTRACT: A stable and isolable difluoromethyl zinc reagent has been prepared through the reaction of ICF_2H with diethyl zinc and DMPU. This new zinc reagent is a free-flowing solid and can be used in combination with a nickel catalyst to difluoromethylate aryl iodides, bromides, and triflates at room temperature. Such mild conditions for the catalytic difluoromethylation of these substrates are unprecedented.

The difluoromethyl group is increasingly important in the life sciences industry.[1,2] The fluorine atoms can modulate hydrophobicities, bestow electronic properties and bioisosteric functionalities, and effect metabolic pathways relative to non-fluorinated parent molecules.[1] Despite the high value of a difluoromethyl group, improvements in late-stage difluoromethylation methodologies are needed. This is especially true for the functionalization of aryl halides, where most of the reported methodologies involve either non-catalytic methods or approaches employing removable protecting groups. For instance, three important methodologies to install difluoromethyl groups from aryl halides are described below. Amii has shown that α-silyldifluoroacetates can be coupled to aryl iodides to afford aryldifluoroacetates in moderate to good yields (Scheme 1, top).[3,4] Under forcing conditions, these difluoroacetates can first be hydrolyzed and then decarboxylated to generate difluoromethyl arene products.[3,4] Hartwig reported an example of direct difluoromethylations using
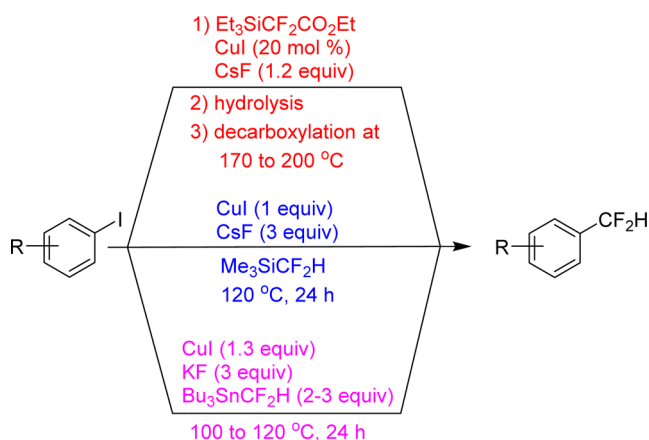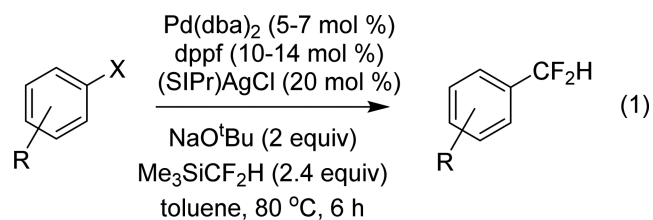
Me_3SiCF_2H as the difluoromethyl source and a stoichiometric amount of copper catalyst at temperatures greater than 100 °C (Scheme 1, middle).[9] Qing later found that the temperature of the reaction could be lowered if *tert*-butoxide was used in place of CsF.[10] Therefore, an obvious disadvantage of these methods is the use of Me_3SiCF_2H,[11] which must undergo reactions at elevated temperatures or with strong nucleophiles in order to cleave the Si−CF$_2$H bond. Tin reagents could also be used for copper-mediated difluoromethylations, and Prakash has reported a complementary protocol outlined in Scheme 1, bottom.[12]

All three of the methods outlined in Scheme 1 use copper to difluoromethylate aryl iodides. In many ways, copper is problematic for this transformation. Ligated $[CuCF_3]$ species are known to display both thermal stabilities and high reactivities, yet related copper(I) difluoromethyl complexes have never been isolated in the solid state. This has prevented fundamental studies on well-defined $[LCu^ICF_2H]$ complexes like those performed on trifluoromethyl analogues.[13] Hartwig suggested that the compatibility of the reaction outlined in Scheme 1 (middle) with high temperatures is due to the formation of a $[Cu(CF_2H)_2]^-$ intermediate, which serves as a stable reservoir of reactive $[Cu(CF_2H)]$.[9] Another argument against the use of copper is that elevated temperatures are required for copper to activate aryl bromides.[14] So in order to develop a mild method that is broader in scope, other transition metals must be explored for their ability to mediate difluoromethylation reactions.

To our knowledge, there is only one report of a method that is catalytic in metal for directly incorporating a difluoromethyl group into aryl halide substrates.[15] As shown in eq 1, this

Scheme 1. Important Synthetic Approaches to Difluoromethyl Arenes[5]

$$
\underset{R}{\text{Ar}}{-}X \xrightarrow[\substack{NaO^tBu\ (2\ equiv) \\ Me_3SiCF_2H\ (2.4\ equiv) \\ toluene,\ 80\ ^oC,\ 6\ h}]{\substack{Pd(dba)_2\ (5\text{-}7\ mol\ \%) \\ dppf\ (10\text{-}14\ mol\ \%) \\ (SIPr)AgCl\ (20\ mol\ \%)}} \underset{R}{\text{Ar}}{-}CF_2H \qquad (1)
$$

method involves the use of expensive palladium and silver co-catalysts, each requiring its own supporting ligand. Moreover, the method uses Me_3SiCF_2H as the difluoromethyl source in combination with the exogenous base sodium *tert*-butoxide as the activator. Considering the inherent aforementioned

disadvantages of the only catalytic method available for this important chemical transformation, we set out to investigate the possibility of reducing such numerous and costly reagents and develop concurrently a base-metal-catalyzed approach.

We first sought to prepare a more convenient difluoromethyl nucleophile. Eujen noted in 1996 that $[CuCF_2H]$, prepared at -30 °C in a mixture of HMPA and diglyme solvents, decomposed readily to 1,1,2,2-tetrafluoroethane (HF_2CCF_2H) upon warming to 10 °C.[16] Burton also reported the decomposition of $[CuCF_2H]$ at low temperatures but noted that the $[Zn(CF_2H)Br]$ analogue, only prepared *in situ*, displayed much better thermal stability, surviving at temperatures of at least 60 °C.[17] We therefore sought to prepare an isolable and user-friendly zinc difluoromethyl reagent that can be used as a nucleophile in screens for metal-mediated cross-coupling reactions. Inspired by literature precedent with perfluoroalkyl substrates,[18−21] we reacted ICF_2H with diethyl zinc in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU), and we were pleased to form $[(DMPU)_2Zn(CF_2H)_2]$ (**1**, eq 2) in high isolated yields as a

$$2\ I{-}CF_2H\ +\ ZnEt_2\ \xrightarrow[94\ \%]{DMPU}\ (DMPU)_2Zn\underset{CF_2H}{\overset{CF_2H}{\diagdown}} \qquad (2)$$

$$\mathbf{1}$$
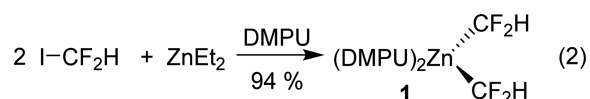
free-flowing solid. Complex **1** is stable in the solid state under an inert atmosphere for months.[22] Single crystals could be grown, and the X-ray data confirm the first example of a solid-state structure of a zinc difluoromethyl complex (Figure 1). The $Zn{-}CF_2H$ bond lengths of 2.045(2) Å are shorter than the average $Zn{-}C$ distance of 2.063(6) Å in $[(pyridine)Zn(CF_3)_2]$,[23] which is the only zinc trifluoromethyl complex in the Cambridge Structural Database.[24]

With the new zinc reagent in hand, we explored its ability to serve as a nucleophile in metal-mediated cross-coupling reactions. Bipyridyl ligands have often been used in combination with nickel in Negishi-like reactions, so this metal/ligand served as a starting point (Table 1, entry 1). Unfortunately, no product was observed by ^{19}F NMR spectroscopy with 4,4′-di-*tert*-butylbipyridine (dtbpy) as a ligand. However, we did observe the formation of $[(dtbpy)Ni(CF_2H)_2]$ (**2**), which was confirmed by X-ray crystallography (Figure 1, bottom). $[(Bipyridyl)Ni(Ar)(X)]$ intermediates are known to undergo redistribution reactions to afford $[(bipyridyl)NiAr_2]$ and $[(bipyridyl)NiX_2]$,[25] and transmetalation of the latter may be the origin of **2**. Another diimine ligand, 1,10-phenanthroline (phen), gave similarly disappointing yields of product (Table 1, entry 2). However, trace amounts of product were detected when 1,1′-bis(diphenylphosphino)-ferrocene (dppf) was used as the ligand (Table 1, entries 3−5). Solvent played a key role (Table 1, entries 6−9), and the optimal conditions identified involved the use of DMSO solvent and nickel precatalyst in 15 mol% (entry 10). The xantphos ligand did not perform as well as dppf (entry 11). Tests using other phosphines are provided in the Supporting Information.

With the optimal conditions identified, we screened the reactivity of the known precatalyst $[(dppf)Ni(COD)]$[26] with a variety of aryl iodides (Table 2). Electron-deficient aryl iodides (Table 2, **3b−3h**) gave difluoromethylated product in good yields, up to 91% for 4-cyano-iodobenzene. Aldehydes, esters, and ketones were all tolerated with this method. Surprisingly, however, the reaction was quite sensitive to electron-donating
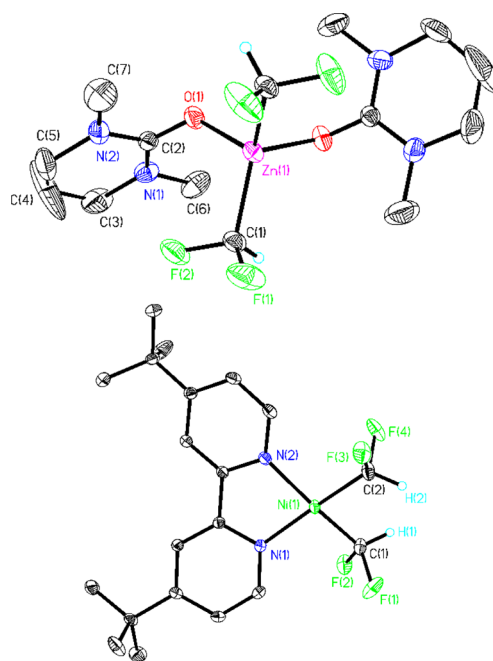

Figure 1. ORTEP diagrams of $[(DMPU)_2Zn(CF_2H)_2]$ (**1**, top) and $[(dtbpy)Ni(CF_2H)_2]$ (**2**, bottom). Selected bond lengths (Å) for **1**: Zn1−C1 2.045(2); Zn1−O1 2.0647(19). Selected bond angles (deg) for **1**: C1−Zn1−C1 134.49(16); C1−Zn1−O1 103.53(9). Selected bond lengths (Å) for **2**: Ni1−C1 1.8845(16); Ni1−C2 1.8867(16); Ni1−N1 1.9495(13); Ni1−N2 1.9671(13). Selected bond angles (deg) for **2**: C1−Ni1−C2 85.26(7); C1−Ni1−N1 97.16(6); C2−Ni1−N1 170.58(6); C1−Ni1−N2 165.95(6); C2−Ni1−N2 97.64(6); N1−Ni1−N2 82.22(5).

Table 1. Results of Catalyst Identification and Optimization[a]

entry	mol % Ni(COD)$_2$	ligand (mol %)	solvent	% yield
1	15	dtbpy (15)	DMSO	0
2	15	phen (15)	DMSO	0
3	10	dppf (10)	toluene	trace
4	10	dppf (10)	dioxane	trace
5	10	dppf (10)	DMPU	trace
6	10	dppf (10)	THF	10
7	10	dppf (10)	MeCN	15
8	10	dppf (10)	DMF	16
9	10	dppf (10)	DMSO	51
10	**15**	**dppf (15)**	**DMSO**	**80**
11	15	xantphos (15)	DMSO	10

[a]All of the reactions were run on a 0.1 mmol scale in 0.5 mL of solvent for 24 h; 1.2 equiv of $[(DMPU)_2Zn(CF_2H)_2]$ was used. The yields of $ArCF_2H$ were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene as an internal standard.
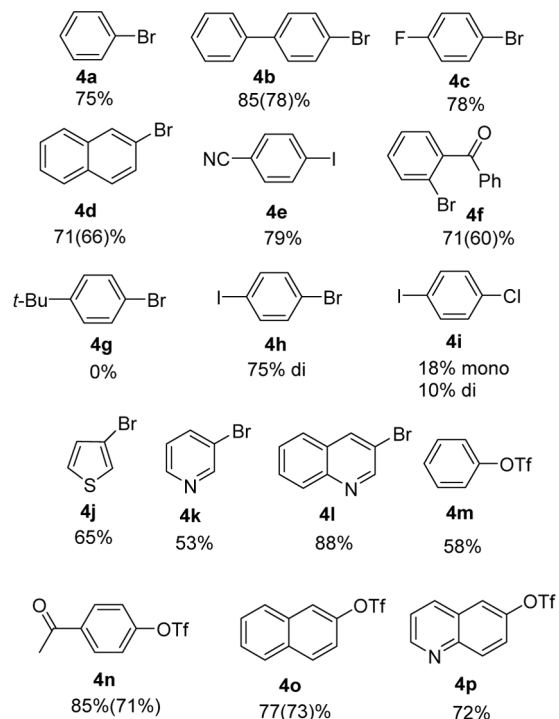
groups, as alkyl groups and ethers gave little to no product (Table 2, **3i−3k**). In a control experiment, we found that stirring a stoichiometric amount of $[(dppf)Ni(COD)]$ with 4-*tert*-butyl iodobenzene for 24 h at room temperature led to no reaction, indicating that the nickel catalyst does not activate substrate under these conditions. Reaction of $[(dppf)Ni(COD)]$ with **3e** under similar conditions led to a new species, which upon addition of **1** produced 4-cyano-1-difluoro-

Table 2. Nickel-Catalyzed Difluoromethylation of Aryl and Heteroaryl Iodides[a]
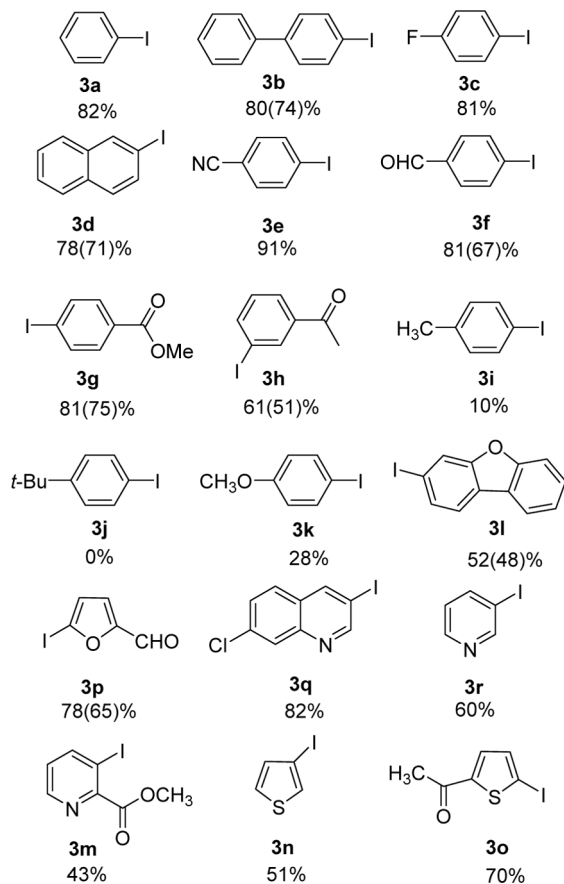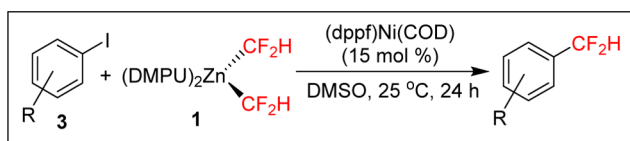
Table 3. Nickel-Catalyzed Difluoromethylation of Aryl Bromides and Triflates[a]

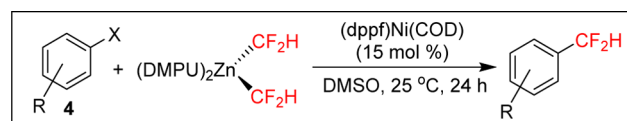[a]The yields of ArCF$_2$H were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene as an internal standard. Isolated yields of nonvolatile products are given in parentheses.

[a]The yields of ArCF$_2$H were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene as an internal standard. Isolated yields of nonvolatile products are given in parentheses.

methylbenzene. An unactivated aryl halide like **3a** produced biphenyl in the absence of the difluoromethyl zinc reagent. Finally, we were pleased to find that oxygen-, nitrogen-, and sulfur-containing heteroaryl iodides (**3l−3o**) did not shut down reactivity and produced difluoromethylated products under the cross-coupling conditions.

Perhaps the most impressive feature of the methodology is the reactivity with aryl bromides. The only other known method for catalytically difluoromethylating aryl bromides operates at 80 °C,[15] whereas the method reported herein operates at room temperature. Table 3 shows that the aryl bromide substrates (**4a−4e**) afford cross-coupled product in yields that are roughly identical to that seen for the aryl iodide counterparts in Table 2. The substrate in Table 3, entry 6, is interesting to consider, as it has previously been used as an intramolecular aryl radical trap.[27] Under photochemical conditions, 2-bromobenzothenone is known to convert to fluorenone in appreciable amounts via the intermediacy of aryl radicals.[27] No fluorenone product was observed by GC-MS when the reaction in entry 6 was monitored by GC-MS. The only other observed byproduct was the debromination product.

A substituent effect was also observed for the aryl bromides whereby simple alkyl substitution led to a dramatic shut-down in reactivity (Table 3, entry 7).

When 4-iodo-1-bromobenzene was used as a substrate, 1,4-bis(difluoromethyl)benzene could be produced in 75% yield (Table 3, entry 8). 4-Iodo-1-chlorobenzene also displayed reactivity, producing the bis-difluoromethylated product in 10% yield (entry 9). Aryl triflates also displayed good reactivity (entries 10−13), and these examples represent, to our knowledge, the first examples of catalytic difluoromethylation of this class of substrate.

In conclusion, a number of important precedents are set in this report. We describe the synthesis of an easy-to-handle and store difluoromethyl complex of zinc. Although stable, this zinc reagent can be used in combination with a base metal to directly and catalytically difluoromethylate aryl iodides, bromides, and triflates. Such substrate scope bodes well for developing a broadly applicable difluoromethylation protocol based on a first-row metal catalyst such as nickel. The identification of a phosphine ligand that could mediate these reactions at nickel provides a starting point to understand how this ligand could be modified to better enable the difluoromethylation of electron-rich aryl halide substrates. While the dppf/nickel combination is known to operate by traditional Ni^0/Ni^{II} redox shuttles in cross-coupling catalysis,[26] recent reports also indicate that odd-electron (dppf)nickel species can readily form under catalytically relevant conditions.[28] To clarify

which redox states of nickel are involved in the Negishi-like reactions reported here, further mechanistic studies are currently being pursued in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00053.

> Experimental procedures, X-ray data, and spectral characterization of all new compounds (PDF)
> X-ray crystallographic data for **1** and **2** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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