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Nickel-Catalyzed Aromatic Cross-Coupling Difluoromethylation of Grignard Reagents with Difluoroiodomethane

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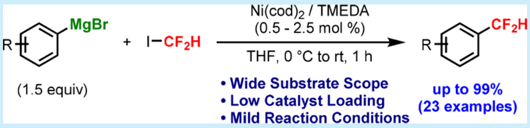
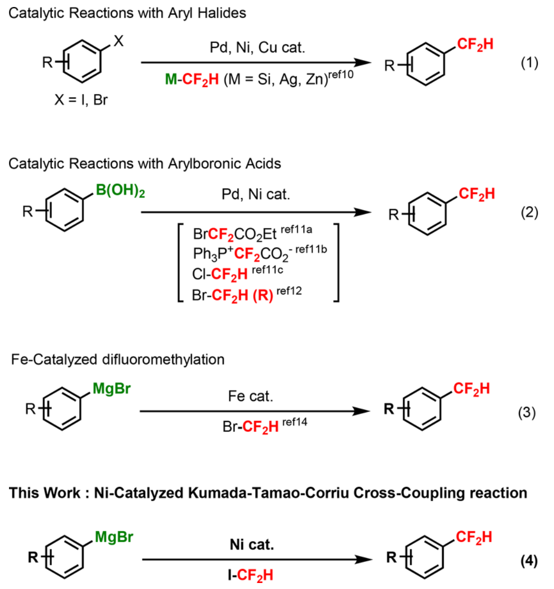
Supporting Information

ABSTRACT: The nickel-catalyzed cross-coupling difluoromethylation of the Grignard reagents with difluoroiodomethane is shown to provide the corresponding aromatic difluoromethyl products in excellent to moderate yields. The difluoromethylation proceeds smoothly within 1 h at room temperature with 1.5 equiv of the Grignard reagents in the presence of Ni(cod)$_2$/TMEDA (2.5−0.5 mol %). Mechanistic studies clarify that the oxidative addition of the Ni(0) catalyst to difluoroiodomethane provides the TMEDA−Ni(II)(CF$_2$H)I complex. This intermediate is transformed to TMEDA−Ni(II)(CF$_2$H)Ph via transmetalation with PhMgBr. The reductive elimination takes place to give the aromatic cross-coupling difluoromethylation product along with regeneration of the TMEDA−Ni(0) catalyst. Electron paramagnetic resonance (EPR) and radical clock analyses of the nickel-catalyzed reaction provide no EPR active Ni(I) and Ni(III) species at around $g = 2$ and only a trace amount of the cyclization product.



Organofluorine compounds have attracted explosive attention in pharmaceutical and agrochemical applications, because fluorinated functional groups confer higher metabolic stability, mimic effect, and lipophilicity, based on their unique chemical, biological, and physical properties.[1] Particularly, a difluoromethyl (CF$_2$H) group can be employed as bioisosteres of alcohol and thiol, which function as lipophilic hydrogen-bonding donors.[2] Therefore, highly efficient synthetic methods to introduce a difluoromethyl group into organic compounds have intensively been developed.[3] Difluoromethylated compounds were synthesized via deoxofluorination of aldehydes with DAST (*N*,*N*-diethylaminosulfur trifluoride) derivatives under harsh reaction conditions, in spite of functional group compatibility.[4] Synthetic methods to provide difluoromethyl arenes via selective benzylic C−H bonds[5] and decarboxylative fluorination of α-fluoroarylacetic acids[6] have also been reported. Recently, direct difluoromethylations through carbon-to-carbon bond formation have appeared.[7−9] However, the development of transition-metal-catalyzed reactions have been quite limited. For example, Pd-, Ni-, and Cu-catalyzed difluoromethylations of aromatic halides with several difluoromethyl metal reagents (M−CF$_2$H: M = Si, Ag, Zn) have been reported (Scheme 1, eq 1).[10] These difluoromethylation reactions generally require high temperature conditions, and the difluoromethyl metal reagents are thermally unstable. Subsequently, cross-coupling reactions using difluoromethyl halides as an electrophile have been reported; metal-difluorocarbene[11] and Suzuki−Miyaura[12] reactions of arylboronic acid with difluoromethyl halide catalyzed by palladium or nickel complexes have been reported (Scheme 1, eq 2). After submitting this paper, Ni-catalyzed radical[13] and Fe-catalyzed[14] difluoroalkylation reactions were reported (Scheme 1, eq 3). However, a conventional and reliable Ni-catalyzed cross-coupling reaction with organomagnesium Grignard reagents of *ubiquitous* synthetic use has never been described.

Scheme 1. Transition-Metal-Catalyzed Aromatic Difluoromethylations



Herein, we wish to report the Ni-catalyzed cross-coupling reaction of the Grignard reagents under mild reaction conditions even at ambient temperature (Scheme 1, eq 4). The mechanism is revealed to involve the Ni(0)/Ni(II) catalytic cycle rather than the Ni(I)/Ni(III) cycle; the

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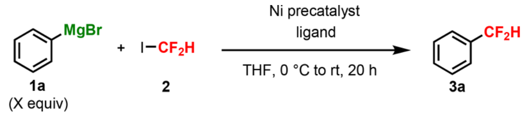
oxidative addition of a $L_nNi(0)$ catalyst to difluoroiodomethane (I−CF_2H), the transmetalation of the Grignard reagents (Ar−MgBr), and the reductive elimination complete a catalytic cycle to afford the difluoromethyl arenes (Ar−CF_2H) and to regenerate the Ni(0) catalyst.

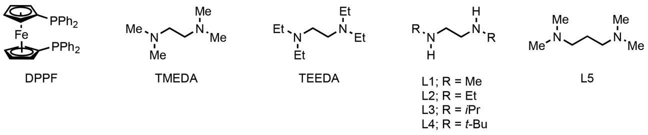
A nickel-catalyzed difluoromethylation reaction of phenylmagnesium bromide **1a** with difluoroiodomethane[15] **2** was carried out (Table 1). No reaction occurred in the absence of either nickel precatalyst or (di)phosphine and amine ligands (entry 1). When 2 equiv of **1a** and difluoroiodomethane were treated with $NiCl_2$ and dppf (10 mol %) in THF at ambient temperature for 20 h, desired product **3a** was generated, albeit in low yield (16%) (entry 2). With TMEDA as a ligand, the yield was improved to 61% (entry 3). Extensive screening of diamine ligands clarified that TMEDA is the best ligand (entries 4−9). A significant improvement in yield up to 99% yield was attained by changing nickel precatalyst from $NiCl_2$ to $Ni(cod)_2$ in combination with the best ligand, TMEDA (entry 10). Reduction of the amount of **1a** to 1.5 equiv did not show any change in yield, but further reduction to just an equimolar amount of **1a** decreased the yield to 59% (entries 11, 12). Even when the amount of the catalyst was reduced to 2.5 mol %, no significant change in yield was observed and the reaction was completed within 5 min (entries 14, 15). The amount of the catalyst could be further reduced to 0.5 mol % to give a quantitative yield (entry 15).

Table 1. Optimization of Difluoromethylation Reactions



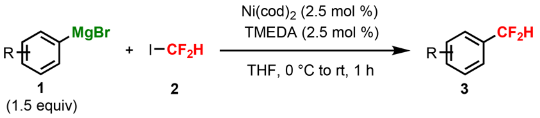
entry	**1a** (*X* equiv)	precatalyst (mol %)	ligand (mol %)	yield (%)[a]
1	2.0	–	–	0
2	2.0	$NiCl_2$ (10)	DPPF (10)	16
3	2.0	$NiCl_2$ (10)	TMEDA (10)	61
4	2.0	$NiCl_2$ (10)	TEEDA (10)	4
5	2.0	$NiCl_2$ (10)	L1 (10)	8
6	2.0	$NiCl_2$ (10)	L2 (10)	8
7	2.0	$NiCl_2$ (10)	L3 (10)	7
8	2.0	$NiCl_2$ (10)	L4 (10)	8
9	2.0	$NiCl_2$ (10)	L5 (10)	16
10	2.0	$Ni(cod)_2$ (10)	TMEDA (10)	>99
11	1.5	$Ni(cod)_2$ (10)	TMEDA (10)	>99
12	1.0	$Ni(cod)_2$ (10)	TMEDA (10)	59
13	1.5	$Ni(cod)_2$ (2.5)	TMEDA (2.5)	>99
14[c]	1.5	$Ni(cod)_2$ (2.5)	TMEDA (2.5)	>99
15[b]	1.5	$Ni(cod)_2$ (0.5)	TMEDA (0.5)	>99

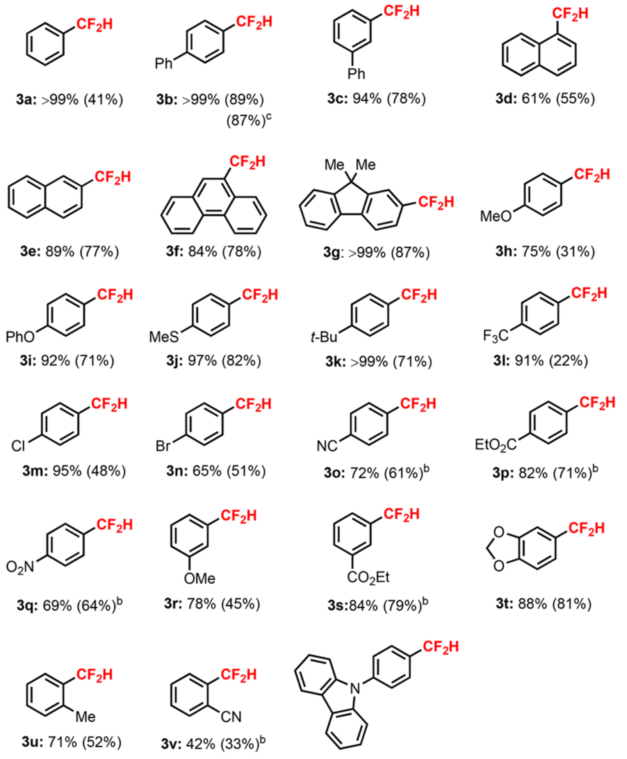
[a] Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. [b] The reaction time was 1 h. [c] The reaction time was 5 min.



Substrate generality was realized under the optimal reaction conditions (2.5 mol % of the Ni precatalyst $Ni(cod)_2$ and the TMEDA ligand, 0 °C to rt 1 h reaction time). Difluoromethylated aryls were synthesized through cross-coupling difluoromethylation of a variety of the Grignard reagents **1** (Table 2).

Table 2. Ni-Catalyzed Difluoromethylation with Grignard Reagents





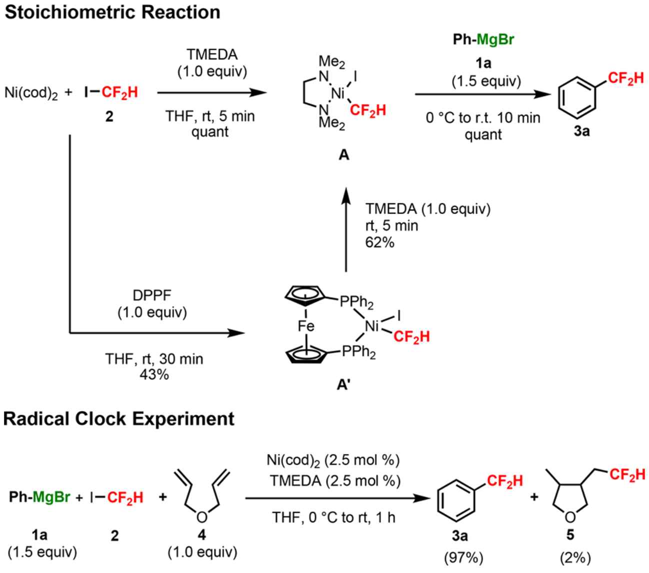
3a: >99% (41%)
3b: >99% (89%) (87%)[c]
3c: 94% (78%)
3d: 61% (55%)
3e: 89% (77%)
3f: 84% (78%)
3g: >99% (87%)
3h: 75% (31%)
3i: 92% (71%)
3j: 97% (82%)
3k: >99% (71%)
3l: 91% (22%)
3m: 95% (48%)
3n: 65% (51%)
3o: 72% (61%)[b]
3p: 82% (71%)[b]
3q: 69% (64%)[b]
3r: 78% (45%)
3s:84% (79%)[b]
3t: 88% (81%)
3u: 71% (52%)
3v: 42% (33%)[b]
3w: >99% (70%)

[a] Reaction conditions: 0.2 mmol of diluoroiodomethane (1.2−1.5 M), 0.3 mmol of ArMgBr (ca. 0.5 M), 2.5 mol % of $Ni(cod)_2$ and TMEDA in 1 mL of THF. Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Isolated yields are shown in parentheses. [b] ArMgBr prepared by the reaction of the corresponding ArI with *i*PrMgBr. [c] Gram-scale synthesis: 10 mmol of diluoroiodomethane, 15 mmol of 4-biphenylmagnesium bromide, 2.5 mol % of $Ni(cod)_2$ and TMEDA in 50 mL of THF. 1.87 g of **3b** was isolated.

Biphenyl, naphthyl, phenanthryl, and fluorenylmagnesium bromide afforded difluoromethylated arenes **3b**−**3g** in good to excellent yields, respectively. Gram-scale synthesis of **3b** was carried out with 10 mmol of difluoroiodomethane **2** and 1.5 equiv of 4-biphenylmagnesium bromide **1b** to give the desired compound **3b** in almost the same yield (87% yield, 1.87 g) as in a small scale reaction. Arylmagnesium bromide with both electron-donating and -withdrawing substituents in the *para*-position showed good reactivity to give desired products **3h**−**3q** in good yields within 1 h. Methoxy and ethoxycarbonyl substituents at the *meta*-position did provide good yields **3r**−**3t**, while a decrease in yield was observed with *ortho*-substituted compounds **3u**−**3v**. Heterosubstituted compounds such as *p*-1-carbazophenylmagnesium bromide afforded product **3w** quantitatively.

The reaction mechanism of a nickel-catalyzed coupling reaction poses a challenge, as highlighted in the Ni(I)/Ni(III) catalytic cycles.[16] A stoichiometric reaction was hence conducted with all components, $Ni(cod)_2$, TMEDA, and difluoroiodomethane, in equal amounts. An oxidative addition intermediate (**A**) was quantitatively observed by ^{19}F NMR (δ_F −107.9, d, J_{F-H} = 51.5 Hz) as compared with the recent report.[13] In order to further clarify the oxidative addition intermediate on the basis of the P−F coupling constant, we employed diphosphine DPPF instead of diamine TMEDA as a ligand. Another oxidative addition intermediate (**A′**) was thus detected by ^{19}F NMR (δ_F −79.7, ap q, $J_{F-H} = J_{F-P}$ = 48.9 Hz).[17] When 1 equiv of TMEDA was added to diphosphine complex **A′**, ligand exchange occurred to give indeed the diamine complex **A**. The Grignard reagent **1a** (1.5 equiv) was then added at 0 °C to give the coupling product **3a** quantitatively at room temperature (Scheme 2).

Scheme 2. Investigation of Reaction Mechanism



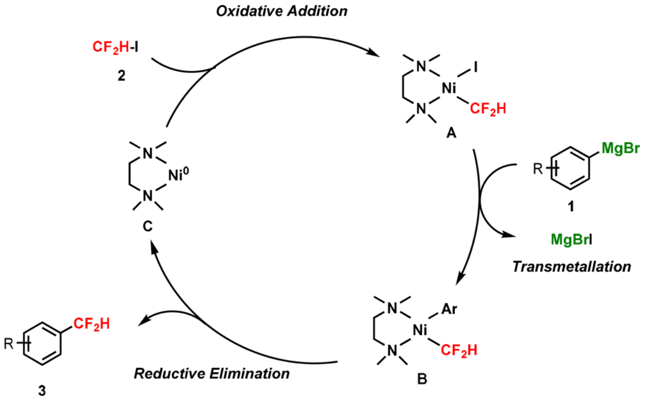
A radical clock experiment was additionally conducted.[12b] When an equimolar amount of diallyl ether **4** was added to the standard catalytic reaction conditions, the same high yield of the difluoromethylated aryl product **1a** was obtained as in the usual difluoromethylation reaction without a radical clock; only 2% of the ring-closing product **5** was obtained with the radical clock, diallyl ether.

Finally, the progress of the nickel-catalyzed difluoromethylation reaction was traced by electron paramagnetic resonance (EPR) spectroscopic analyses; EPR active chemical species such as Ni(I) and Ni(III) complexes at around *g* = 2 were not observed at all.[18−21] These results indicate Ni(I) or Ni(III) species are not involved in this nickel-catalyzed difluoromethylation.

Based on these results, a plausible reaction mechanism is visualized for construction of the Ni(0)/Ni(II) catalytic cycle rather than the Ni(I)/Ni(III) or radical cycles (Scheme 3). Initially, the oxidative addition of difluoroiodomethane to TMEDA−Ni(0) (**C**) leads to **A** at room temperature. Subsequently, the transmetalation of the aryl Grignard reagent **1** to produce **B** and finally the reductive elimination thereof afford the desired aromatic cross-coupling difluoromethylation products **3**.

In summary, we have succeeded in the development of the cross-coupling difluoroiodomethylation of organomagnesium reagents with difluoroiodomethane in the presence of the Ni catalyst under the mild reaction conditions even at ambient temperature. It has been mechanistically clarified that the oxidative addition of the Ni(0) catalyst to I−CF$_2$H provides a TMEDA−Ni(II)(CF$_2$H)I complex and that Ni(Ar)CF$_2$H generated by transmetalation promotes the final reductive elimination. EPR and radical clock analyses of the nickel-catalyzed reaction provide no ERR active Ni(I) species at around *g* = 2 and only a trace amount of a cyclization product. The plausible reaction mechanism is thus visualized for construction of the Ni(0)/Ni(II) catalytic cycle rather than the Ni(I)/Ni(III) or radical cycles. Development of practical and reliable catalytic difluoromethylation reactions using other difluoromethylating and organometallic reagents under transition-metal catalysis is in progress.

Scheme 3. Plausible Catalytic Cycle



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02264.

Experimental procedures, compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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