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Nickel-Catalyzed Negishi Cross-Coupling of Bromodifluoroacetamides

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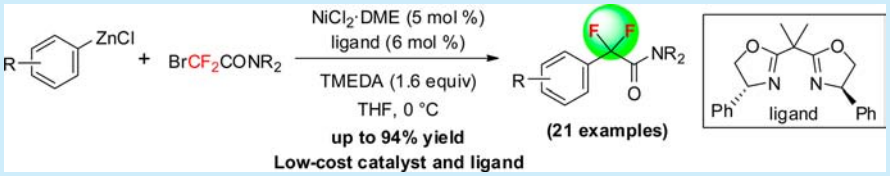
Supporting Information



ABSTRACT: A nickel-catalyzed Negishi coupling of bromodifluoroacetamides with arylzinc reagents has been developed. This reaction allows access to difluoromethylated aromatic compounds containing a variety of aryl groups and amide moieties. Furthermore, highly effective transformation of the functionalized difluoromethyl group ($-CF_2CONR^1R^2$) was realized via microwave-assisted reduction under mild conditions. The notable features of this strategy are its generality and its use of a low-cost nickel catalyst and ligand; thus, this reaction provides a facile method for applications in drug discovery and development.

Fluorine-functionalized aromatic compounds are of great importance in both the life and materials sciences.[1] Among such compounds, molecules containing an α,α-difluorobenzyl unit ($ArCF_2-$) are especially desirable structures for use in medicinal chemistry because the two fluorine atoms are contained at a metabolically labile benzylic position.[2] Additionally, the difluoromethyl carboxylic acid structures ($CF_2CONR^1R^2$, CF_2CO_2Et, and $CF_2PO(OEt)_2$) are very attractive structures, as the functionalized difluoromethyl group can be easily transformed into other fluorine-containing groups because of the strong electrophilicity of the CF_2-carbonyl group.[3] The use of a copper difluoroacetate reagent[4] and the copper-catalyzed cross-coupling reaction[5−7] are among the most well-known methods for the functionalized fluorination of arenes. During the past few years, such functionalized fluorinations have been achieved using transition-metal-catalyzed cross-coupling reactions and visible-light photoredox reactions.[3,8−10] However, these reported coupling reactions need an expensive palladium catalyst and complex ligands or require as fluorinated building blocks trimethylsilyl difluoroacetic acid derivatives that are not commercially available. It also can be difficult to control the regioselectivity of the product using multisubstituted substrates in the visible-light-induced reaction. Therefore, convenient methods for the introduction of a functionalized CF_2 group to arenes remain scarce. We recently reported the cross-coupling reaction of fluorinated β-lactams with arylmetal species in the presence of a nickel catalyst.[11] We hypothesized that the synthesis of functionalized difluoromethylated arenes could be realized using a bromodifluoroacetic acid derivative instead of a fluorinated β-lactam. However, the reductive elimination of the fluoroalkylmetal complex is slower than that of nonfluorinated analogues.[12] Furthermore, it is more difficult to achieve reductive elimination from a nickel complex than from a palladium complex.[13] To the best of our knowledge, there has been only one report on the introduction of CF_2-carboxylic acid structures to aromatics using a nickel catalyst, from Zhang and cowokers;[14] therefore, the cross-coupling of a bromodifluoroacetic acid derivative using a nickel catalyst is attractive.[15] Herein we report the nickel-catalyzed cross-coupling reaction of bromodifluoroacetamides with arylzinc reagents. In a further demonstration of the synthetic utility of this method, we have also addressed the transformation of the fluoroalkyl chain on the arylated product.

We initiated our studies of the nickel-catalyzed α-arylation of an α,α-difluoroacetic acid derivative by evaluating the reaction of bromodifluoroacetamide **1** with an arylzinc reagent. With a combination of 5 mol % $NiCl_2$·DME and 6 mol % bisoxazoline ligand, the reaction of **1** with 4-methoxyphenylzinc chloride (**2b**) gave the corresponding product **3b** in 86% yield (Table 1, entry 1). On the basis of Inoue's report,[8] a stoichiometric amount of tetramethylethylenediamine (TMEDA) with respect to the amount of arylzinc reagent was used as an additive; however, the yield of **3b** was decreased, and **1** was recovered in 52% yield (Table 1, entry 2). A half equivalent of TMEDA was effective in the reaction, providing a 91% yield of **3b** (Table 1, entry 3). Decreasing the loading of **2b** led to a lower yield of **3b** (Table 1, entries 4 and 5). When the reaction of arylzinc reagent **2b** with ethyl bromodifluoroacetate instead of **1** was examined, the corresponding α-aryl-α,α-difluoroacetate was obtained in only 42% yield with no recovery of bromodifluoroacetate (Scheme 1). This suggested that the high electrophilicity of the CF_2-ester moiety led to decomposition of the bromodifluoroacetate. Thus, bromodifluoroacetamides are suitable for this Negishi cross-coupling reaction. Although we screened other ligands and

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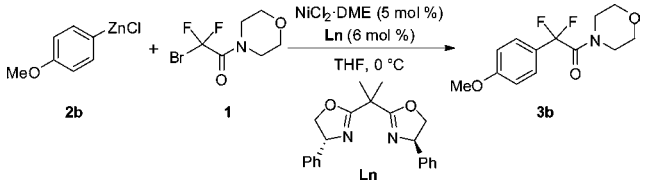
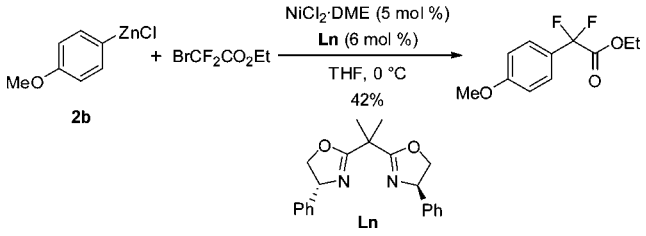
Table 1. Optimization of the Nickel-Catalyzed Arylation of Bromodifluoroacetamide



entry	equiv of **2b**	additive (equiv)	time (h)	**3b**/**1** yield (%)
1	3	–	0.5	86/–
2	3	TMEDA (3)	3	11/52
3	3	TMEDA (1.6)	0.5	91/–
4	1.5	TMEDA (0.8)	3	80/10
5	1.2	TMEDA (0.6)	3	68/28

Scheme 1. Reaction of Ethyl Bromodifluoroacetate with 2b

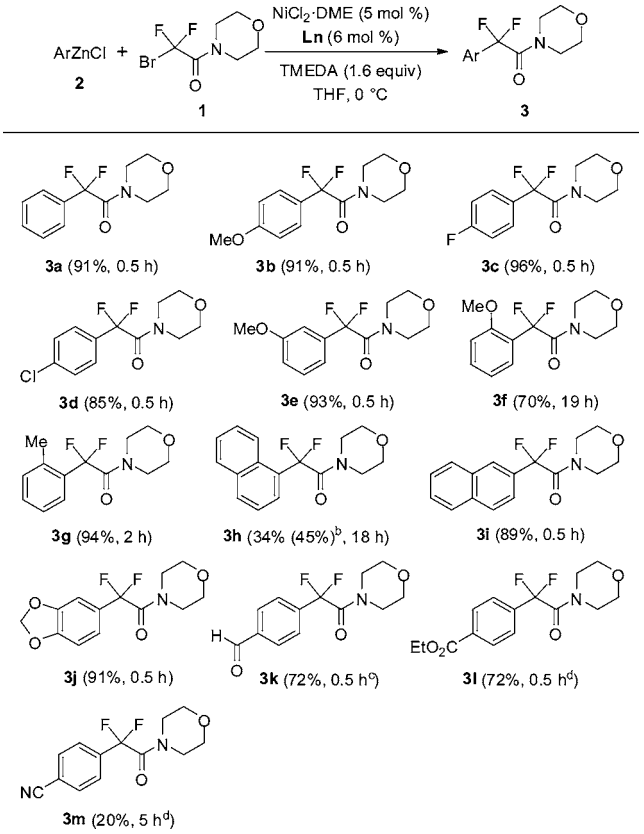


solvent systems, no improvement in the product yields was observed (for details, see the Supporting Information).

With the optimized reaction conditions in hand, a wide variety of arylzinc reagents were investigated for use in this method (Scheme 2). Generally, electron-rich and electron-neutral arylzinc reagents provided the corresponding α-aryldifluoroacetamides in high yields (**3a**–**d**, **3i**, and **3j**). Meta and ortho substituents on the arylzinc reagents did not affect the reaction yield and afforded the coupled products in high yields (**3e**–**g**). However, the highly sterically hindered arylzinc reagent **2h** was not a suitable substrate, providing the product in low yield together with the recovery of **1** in 45% yield. Importantly, versatile ester and nitrile functional groups were tolerated rather well (**3l** and **3m**). Arylzinc reagent **2k** with an acetal group was also a suitable coupling partner, providing the acetal-deprotected product **3k** in good yield. In contrast to previously reported difluoromethylations of aromatics,[9,13] our nickel-catalyzed α-arylation of bromodifluoroacetamides progressed smoothly in a short time and at low temperature, except for ortho-substituted substrates. However, alkyl and heteroarylzinc reagents did not provide the corresponding coupled products.

To further demonstrate the generality of this reaction, the structurally diverse bromodifluoroacetamides **4**–**11** were prepared, and their reactions with arylzinc chlorides were examined.[16] The results are summarized in Scheme 3. Both cyclic and acyclic *N*,*N*-dialkylamides were suitable as coupling partners, giving the corresponding products in high yields (**12b**, **13a**, **14a**). As piperizine- and *N*-arylpiperazineamides are featured as substructures in many bioactive compounds, these successful results are of particular significance for drug discovery.[17] In addition, *N*-hydrogen-containing bromodifluoroacetamides could also be used for this coupling to afford the corresponding products (**15a**, **16a**, **17a**, **18a**, **19a**). However, when the reaction of *N*-unsubstituted bromodifluoroacetamide was conducted using 3 equiv of phenylzinc chloride, the coupling product (**17a**) was obtained only in low yield (36%). The same

Scheme 2. Nickel-Catalyzed Negishi Coupling of Bromodifluoroacetamide 1 with Arylzinc Chlorides[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (3 equiv), THF (5 mL). [b]The yield of **1** is shown in parentheses. [c](4-(Diethoxymethyl)phenyl)zinc chloride was used as the arylzinc reagent. [d]The arylzinc chloride was prepared via Knochel's direct zincation in the presence of magnesium.

reaction using 5 equiv of phenylzinc chloride gave the desired product in moderate yield (47%). In addition, a phenylalanine derivative afforded the peptidyl coupling product **18a**, but an aniline derivative gave the corresponding coupling product **19a** in only 13% yield, with the aniline derivative recovered in 78% yield. This suggests that acidic *N*-arylamides suppress the coupling process.

To demonstrate the synthetic utility of the products obtained in the reaction, we examined the reduction of α-aryl-α,α-difluoroacetamide **3b** to give amine **20**. Following Hartwig's report on the borane reduction of α-aryl-α,α-difluoroacetamides,[3] we attempted the reduction of α-aryl-α,α-difluoroacetamide **3b** using borane as the reductant. The reaction of **3b** with the BH_3–THF complex was carried out in CH_2Cl_2 with heating and provided the corresponding amine **20** without hydrodefluorination. Despite the long reaction time (26 h), the moderate yield of **20** was not improved, and the starting material **3a** was recovered (Scheme 4).[18] However, when microwave heating was applied to this reaction, the reduced product **20** was obtained in 88% yield after only 20 min, and no side product was observed under these reaction conditions.[19]

In conclusion, we have developed a convenient method for the synthesis of α-aryl-α,α-difluoroacetamides via a nickel-catalyzed Negishi coupling reaction. This coupling reaction allows access to difluoromethylated aromatics containing a variety of aryl groups and amide moieties. Further structural conversion of the CF_2–amide was realized by microwave-assisted borane reduc-

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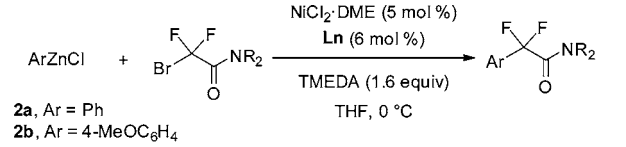
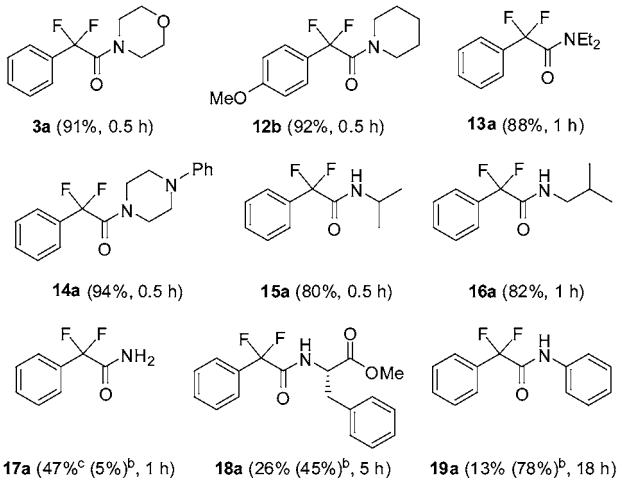
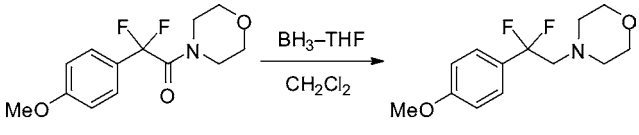
Scheme 3. Scope of Bromodifluoroamides for This Reaction[a]





[a]Reaction conditions: Bromodifluoroacetamide (0.5 mmol), **2** (3 equiv), THF (5 mL). [b]The yield of the bromodifluoroacetamide is shown in parentheses. [c]5 equiv of **2a** and 2.6 equiv of TMEDA were used.

Scheme 4. Transformation of α-Aryl-α,α-difluoroacetamide 3b



reaction conditions	temp (°C)	time	yield of **20** (%)
conventional heating	reflux	26 h	66 (26)[a]
μW	130	20 min	88

[a]The yield of **3b** is shown in parentheses.

tion to provide the corresponding amine under mild conditions. This nickel-catalyzed Negishi coupling reaction could provide a new synthetic strategy for drug discovery, and further investigation of this protocol toward the synthesis of bioactive fluorinated compounds is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00232.

General information, detailed experimental procedures for the starting materials and the products, and characterization of all products, including ^{1}H, ^{13}C, and ^{19}F NMR spectra of the compounds (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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