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Tandem Difluoroalkylation-Arylation of Enamides Catalyzed by Nickel

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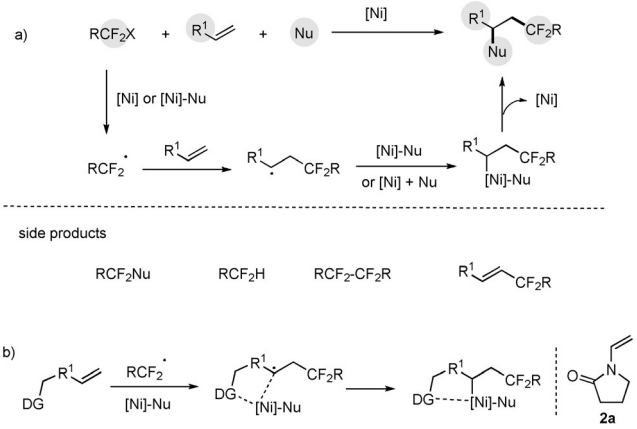
Abstract: *A nickel-catalyzed three-component reaction for the synthesis of difluoroalkylated compounds through tandem difluoroalkylation-arylation of enamides has been developed. The reaction tolerates a variety of arylboronic acids and widely available difluoroalkyl bromides, and even the relatively inert substrate chlorodifluoroacetate. The significant advantages of this protocol are the low-cost nickel catalyst, synthetic convenience, excellent functional-group compatibility and high reaction efficiency.*

The development of new and efficient methods for the synthesis of difluoroalkylated compounds have received great attention recently because of the unique properties of difluoromethylene group (CF_2)[1] and its important applications in medicinal chemistry.[2] Although significant progress in this field has been achieved over the past few years, almost all the effort mainly focused on the construction of a carbon–difluorocarbon bond (C–CF_2) by two-component reactions.[3] Conceptually, the introduction of a CF_2 group into organic molecules through a multicomponent reaction would be a more efficient and synthetically convenient strategy to access difluoroalkylated compounds, in particular for those compounds which are difficult to prepare through conventional methods. Very recently, we reported a nickel-catalyzed difluoroalkylation of arylborons with difluoroalkylbromides, in which a difluoroalkyl radical from a single-electron pathway (SET), is involved in the reaction.[4–7] Inspired by this preliminary study,[4] we envisioned the feasibility of a nickel-catalyzed radical tandem process for the synthesis of difluoroalkylated compounds through a three-component reaction. Our design is based on the hypothesis that a difluoroalkyl radical is induced by a nickel complex and is then trapped by an alkene, with a subsequent cross-coupling leading to a difluoroalkylated molecule having two new C–C bonds and a new chiral center (Scheme 1 a). However, such a hypothetical reaction is complicated by a number of potential side reactions, such as cross-couplings between two coupling partners, dehalohydrogenation or dimerization of difluoroalkyl halides, β-hydride elimination from the alkyl metal intermediates, and so on. As a result, it is extremely difficult to realize such a strategy. To date, an example of such a strategy for accessing fluorinated compounds has not been reported.[8] Even for nonfluorinated substrates, only one example has been reported during our manuscript preparation.[9] We have therefore sought after a system to resolve these substantial challenges. Herein, we describe the first example of a nickel-catalyzed three-component reaction for the synthesis of difluoroalkylated compounds through tandem difluoroalkylation-arylation of enamides, and it tolerates a variety of low-cost and widely available difluoroalkyl bromides/chlorides and arylboronic acids.



Scheme 1. Hypothesis for a nickel-catalyzed difluoroalkylation reaction from difluoroalkyl halides.

According to the hypothesis, our solution to the substantial challenges of such a strategy is based on the consideration that if an alkene can trap the difluoroalkyl radical (RCF_2·) faster than the nickel complex ([Ni] or [Ni]-Nu) reacts with RCF_2·,[10] and with the aid of a coordinating group on the alkene to chelate the nickel complex and facilitate its recombination with the newly formed alkyl radical, it would be feasible to access the final product and avoid the formation of some other side products (Scheme 1 b). To fulfill this approach, a commercially available, electron-rich alkene enamide (**2a**) with a carbonyl group as a chelating group, was employed. Furthermore, the resulting β-difluoroalkylated amines are an important structural motif in medicinal chemistry, but efficient methods to access such valuable structures are limited.[11]

Accordingly, we began by choosing the low-cost and widely available bromodifluoroacetate ($BrCF_2CO_2Et$; **1a**), enamide **2a**, and the air-stable arylbronic acid **3a** as model substrates (Table 1). After a survey of the ligands, it was found that a range of yields (53–69 %) of the α,α-difluoro-γ-amino acid **4a** could be obtained through a combination of $NiCl_2$·DME (5 mol %) with some diamine ligands in the

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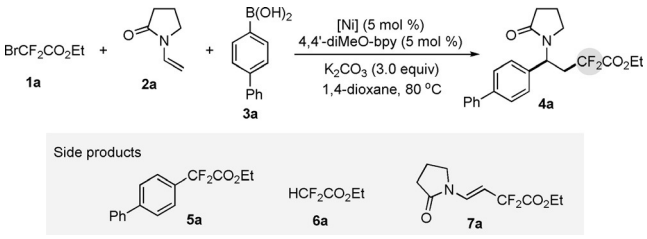
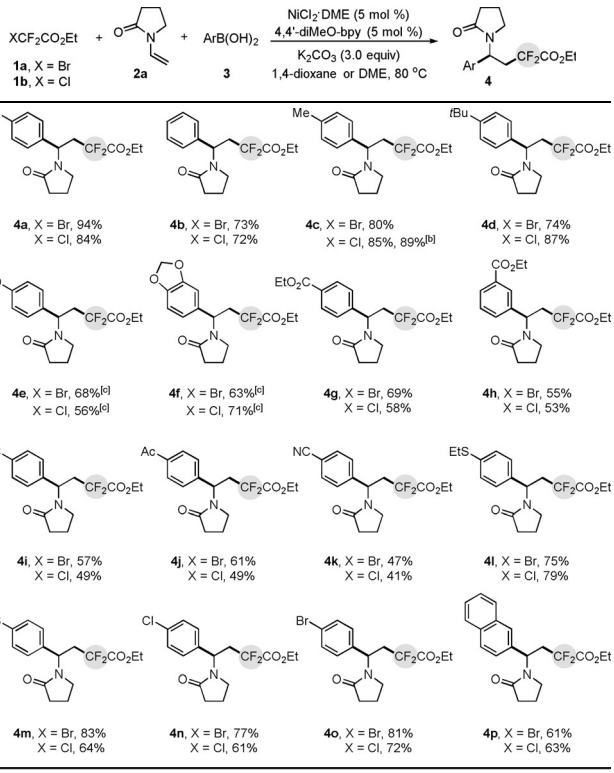
Table 1: Representative results for optimization of the nickel-catalyzed difluoroalkylation-arylation of **2a**.[a]



Entry	**1a**/**2a**/**3a** (equiv)	[Ni]	Yield [%][b] **4a**	**5a**	**6a**	**7a**
1	1/1/2	$NiCl_2$·DME	69	10	2	–
2	1.5/1/2	$NiCl_2$·DME	77	24	5	6
3	1.5/1/2	$NiCl_2$·$(PPh_3)_2$	49	36	13	7
4	1.5/1/2	$NiCl_2$·(dppf)	23	24	6	55
5	1.5/1/2	$Ni(NO_3)_2$·$6H_2O$	67	33	5	7
6	1.5/1/2	$Ni(OTf)_2$	64	30	2	5
7	1.5/1/2	$Ni(COD)_2$	55	27	5	11
8	1.5/1/1.5	$NiCl_2$·DME	77	16	4	7
9[c]	1.5/1/1.5	$NiCl_2$·DME	(94)	n.d.	n.d.	n.d.
10	1.5/1/1.5	–	n.r.	n.r.	n.r.	n.r.

[a] Reaction conditions (unless otherwise specified): **1a** (1.0–1.5 equiv), **2a** (0.2 mmol, 1.0 equiv), **3a** (1.5–2.0 equiv), [Ni] (5 mol%), 4,4′-diMeO-bpy (5 mol%), and K_2CO_3 (3.0 equiv), 1,4-dioxane (2 mL), 80°C, 24 h. [b] Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. Value within parentheses is yield of the isolated product. [c] DME was used as the solvent. bpy = 2,2′-bipyridine, DME = 1,2-dimethoxyethane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene), n.d. = not determined, n.r. = no reaction, Tf = trifluoromethanesulfonyl.

Table 2: Nickel-catalyzed difluoroalkylation-arylation of **2a** with bromo/chlorodifluoroacetate and the arylboronic acids **3**.[a]



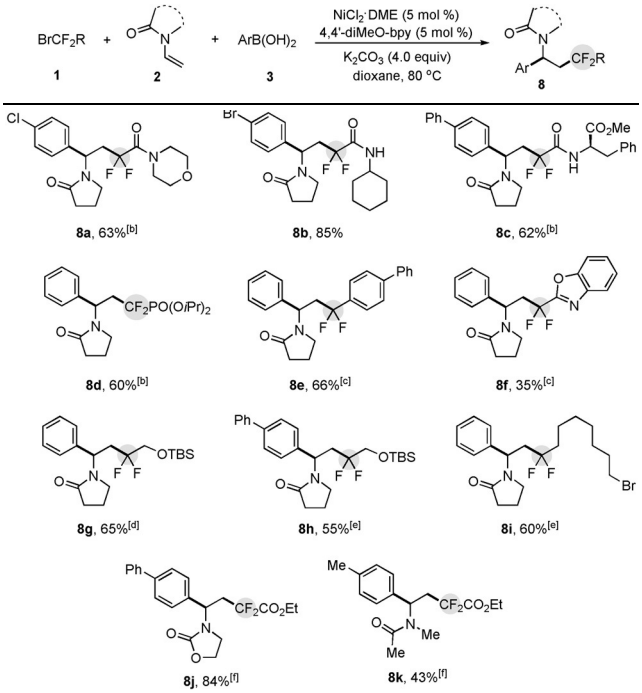
[a] Reaction conditions (unless otherwise specified): **1** (0.6 mmol, 1.5 equiv), **2a** (0.4 mmol, 1.0 equiv), **3** (0.6 mmol, 1.5 equiv), 80°C, 24 h. All reported yields are those of the isolated products. [b] Gram-scale synthesis. [c] **1** (0.6 mmol, 1.5 equiv), **2a** (0.4 mmol, 1.0 equiv), **3** (0.8 mmol, 2.0 equiv), $NiCl_2$·DME (5 mol%), bpy (5 mol%), 1,4-dioxane (4 mL), 80°C, 24 h.

presence of K_2CO_3 in 1,4-dioxane at 80°C (for details see the Supporting Information). And 4,4′-diMeO-bpy proved to be the superior ligand, thus providing **4a** in 69% yield along with some side products [the aryldifluoroacetate **5a** (10% yield) and hydrodebrominated product **6a** (2% yield); entry 1]. But the triamine ligands terpyridine and Pybox failed to provide **4a**. The ratio of **1a**/**2a**/**3a** and the nickel sources are critical to the reaction efficiency (for details see the Supporting Information). Increasing the amount of **1a** benefited the reaction efficiency, but the yield of **5a** was increased and accompanied by the Heck-type product **7a** (entries 2–8). Among the tested nickel catalysts, $NiCl_2$·DME was still the best choice. Other nickel sources, such as $[NiCl_2(PPh_3)_2]$, $[NiCl_2(dppf)]$, and $[Ni(COD)_2]$ led to lower yields of **4a** and increased yields of **5a** and **7a** (for details see the Supporting Information). Finally, the optimized reaction conditions were identified by switching the solvent from 1,4-dioxane to 1,2-dimethoxyethane (DME), and 94% yield of **4a** could be obtained when the reaction was carried out with **1a** (1.5 equiv), **2a** (1.0 equiv), **3a** (1.5 equiv), $NiCl_2$·DME (5 mol%), 4,4′-diMeO-bpy (5 mol%), and K_2CO_3 (3.0 equiv) in DME at 80°C (entry 9). No desired product was obtained without either the nickel catalyst or ligand (entry 10), thus demonstrating the essential role of nickel catalyst in promoting the reaction.

To ascertain the substrate scope of this method, a variety of arylboronic acids were investigated and provided the α,α-difluoro-γ-amino acid derivatives **4** in moderate to high yields when **1a** was employed as a coupling partner (Table 2). Many versatile functional groups, such as alkoxycarbonyl, formyl, enolizable ketone, cyano, thioether, and silyl groups showed excellent compatibility in the reaction (**4g**–**m**). In addition, the successful formation of **4n** and **4o** in good yields with intact chloride and bromide groups provide good opportunities for downstream transformations. Most remarkably, chlorodifluoroacete ($ClCF_2CO_2Et$; **1b**) was also applicable to the reaction when 1,4-dioxane was used as a solvent, and even higher yields of **4** were provided in some cases (**4c**, **4d**, **4f**, and **4l**), thus demonstrating the advantages of this catalytic system. It is also possible to access the desired product on gram-scale through current process. For example, a yield as high as 89% was obtained for the gram-scale synthesis of **4c**. In light of the abundance of fluoroalkyl chlorides (R_f–Cl) in raw industrial materials, we believe that this process will prompt the research in fluoroalkylation reactions with R_f–Cl.

In addition to demonstrating the substrate scope of this reaction, a variety of difluoroalkyl bromides were examined (Table 3). Good yield was obtained when bromodifluoroacetamide was examined (**8a**). The protic amide did not interfere with the reaction efficiency, and even higher yield was afforded (**8b**). Although a mixture of diastereoisomers in a 1:1 ratio was provided when amino-acid-derived bromodifluoroacetamide was used as a coupling partner, these two

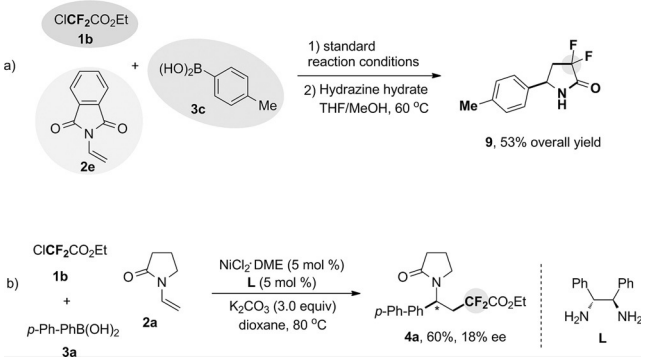
Table 3: Nickel-catalyzed difluoroalkylation-arylation of **2** with the difluoroalkyl halides **1** and arylboronic acids **3**.[a]



[a] Reaction conditions (unless otherwise specified): **1** (0.8 mmol, 2.0 equiv), **2a** (0.4 mmol, 1.0 equiv), **3** (0.8 mmol, 2.0 equiv), $NiCl_2$·DME (5 mol%), 4,4′-diMeO-bpy (5 mol%), and K_2CO_3 (4.0 equiv), 1,4-dioxane (4 mL), 80°C, 48 h. [b] $NiCl_2$·DME (8 mol%) and 4,4′-diMeO-bpy (8 mol%). [c] **1** (0.6 mmol, 1.5 equiv), **2a** (0.4 mmol, 1.0 equiv), **3** (0.6 mmol, 1.5 equiv) and K_2CO_3 (3.0 equiv), 1,4-dioxane (4 mL), 80°C, 24 h. [d] $NiCl_2$·DME (8 mol%), 4,4′-di*t*Bu-bpy (8 mol%). [e] $NiCl_2$·DME (5 mol%), 4,4′-di*t*Bu-bpy (5 mol%). [f] $ClCF_2CO_2Et$ was used as a substrate and 3.0 equiv of K_2CO_3 was used. TBS = *tert*-butyldimethylsilyl.

isomers could be easily resolved by flash chromatography (**8c**). The difluoroalkyl bromide can also be extended to a bromodifluoromethylphosphonate (**8d**). Given that the phosphonyldiflluoromethyl group [$CF_2PO(OR)_2$] has important applications in medicinal chemistry, this transformation may have potential applications in drug discovery and development. Furthermore, aryldifluoromethyl bromide and bromodifluoromethylated benzoxazole were also applicable to the reaction (**8e** and **8f**). Although 35% yield of **8f** was provided, a multistep procedure to prepare such a structure would be required if conventional methods was used. Remarkably, the unactivated 1-bromo-1,1-difluoroalkanes were also viable in the reaction, thus providing **8g–i** with good yields. The chemoselective reaction of the Br–CF_2 bond with **2a**, with an intact Br–CH_2 bond, proceeded smoothly, thus demonstrating that the difluoroalkyl bromide is more reactive than its nonfluorinated counterpart. This result may be ascribed to the high electronegativity of the fluorine atom, which makes it easier for the difluoroalkyl bromide to accept an electron relative to its nonfluorinated counterpart.[12] The reaction was not restricted to **2a**, as 3-vinyloxazolidin-2-one (**2b**) was also a suitable substrate and provided the corresponding product **8j** in good yield. Furthermore, the acyclic enamide **2c** was amenable to the reaction conditions and provided **8k** in a synthetically useful yield. However, the 1,2-substituted enamide (*E*)-1-(prop-1-en-1-yl)pyrrolidin-2-one (**2d**) led to some uncertain side products.

The significant advantages of this strategy can be demonstrated by the rapid synthesis of biologically active molecules in a one-pot reaction. As shown in Scheme 2a, after the commercially available 2-vinylisoindoline-1,3-dione **2e** was

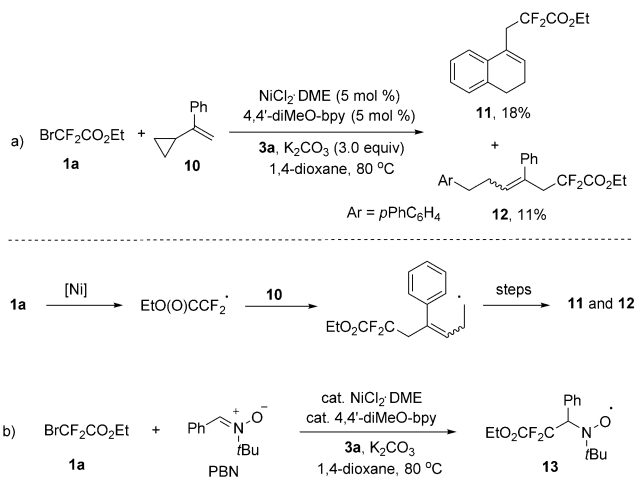


Scheme 2. Reactions with the enamides **2** and stereoconvergent synthesis of compound **4a**. THF = tetrahydrofuran.

treated with **1b** and the arylboronic acid **3c** under standard reaction conditions, the resulting β-difluoroalkylated amino acid ester was subsequently deprotected by hydrazine and subsequent cyclization produced the lactam **9** with high efficiency (53% overall yield). This highly efficient procedure highlighted the four-step synthesis in a one-pot reaction, and formation of two new C–C bonds, one new amide bond, and a chiral center, thus demonstrating the synthetic convenience and utility of current process. Because **9** is an important fluorinated structure in the drug discovery and development,[13] we view this transformation as a facile route for applications in organic synthesis and medicinal chemistry.

Most importantly, the utility of this protocol can also be demonstrated by its potential to stereoselectively synthesize difluoroalkylated compounds. As shown in Scheme 2b, **4a** can be stereoconvergently prepared in 18% *ee* under standard reaction conditions with a chiral diamine ligand. Although low enantioselectivity is observed, it provides a good opportunity for catalytic, enantioselective synthesis of difluoroalkylated molecules through nickel-catalyzed cross-coupling.[14] It should be mentioned that no enantioselective nickel-catalyzed three-component reaction has been reported so far. Thus, we believe that this method will prompt the research in nickel-catalyzed asymmetric synthesis.

To probe whether a difluoroalkyl radical exists in the reaction, radical inhibition experiments (for details see the Supporting Information) and a radical-clock experiment were performed. When **1a** was treated with α-cyclopropylstyrene[15] (**10**) in the presence of **3a** under the standard reaction conditions, the ring-expanded product **11** was formed in 18% yield (Scheme 3a). The product **12** was also obtained in 11% yield, thus indicating that a difluoroalkyl radical is involved in the reaction process and the pathway hypothesized in Scheme 1a is reasonable. The formation of a radical inter-



Scheme 3. Experiments to trap the difluoroalkyl radical.

mediate was further confirmed by an ESR study of reaction of **1a** with the spin-trapping agent phenyl *tert*-butyl nitrone (PBN) in the presence of **3a** (Scheme 3b), in which EtOC(O)CF_2CHPhN(O·)-*t*Bu (**13**) was produced as a spin adduct of the trapped EtOC(O)CF_2· radical. Thus, these results clearly demonstrate that a free fluoroalkyl radical is involved in the reaction.

In conclusion, the first example of a nickel-catalyzed tandem difluoroalkylation-arylation of enamides with widely available difluoroalkyl halides by a three-component reaction has been developed. The reaction tolerates a variety of arylboronic acids and difluoroalkyl bromides, even the "inert" chlorodifluoroacetate is a competent coupling partner, thus featuring the generality of this protocol. The efficient formation of α,α-difluoro-lactam provides a facile route for applications in drug discovery and development. Because of its low-cost nickel catalyst, synthetic simplicity, excellent functional-group compatibility, and high reaction efficiency, we believe this nickel-catalyzed three-component reaction will prompt research in cost-efficient synthesis of fluoroalkylated compounds from simple substrates. Importantly, this nickel-catalyzed radical/cross-coupling process also provides a good opportunity for catalytically enantioselective synthesis of difluoroalkylated compounds. Further studies to explore the derivative reactions, as well as the asymmetric synthesis of fluorinated compounds through this strategy are now in progress in our laboratory.

Acknowledgements

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Keywords: boron · cross-coupling · fluorine · nickel · synthetic methods

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