Synthetic Methods

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Nickel-Catalyzed Decarboxylative Difluoroalkylation of α,β-Unsaturated Carboxylic Acids

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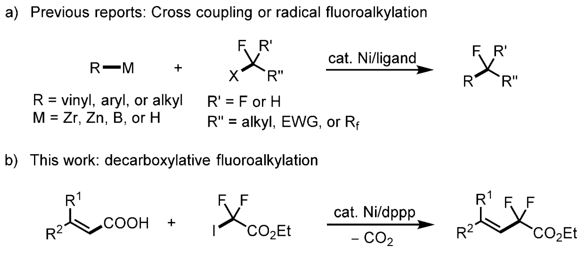
Abstract: *The first example of nickel-catalyzed decarboxylative fluoroalkylation of α,β-unsaturated carboxylic acids has been developed with commonly available fluoroalkyl halides. This novel transformation has demonstrated broad substrate scope, excellent functional-group tolerance, mild reaction conditions, and excellent stereoselectivity. Mechanistic investigations indicate that a fluoroalkyl radical is involved in the catalytic cycle.*

The incorporation of fluorine into organic compounds can often remarkably enhance the lipophilicity, metabolic stability, and bioavailability of the parent molecules.[1] As a result, fluorine-containing compounds have been widely used in pharmaceuticals and agrochemicals, as well as in materials and life sciences,[2] and the selective introduction of fluorine or a fluorine-containing group into drug candidates has long been recognized as a powerful strategy in drug design and screening. Hence, considerable and persistent efforts have been devoted to developing practical and efficient methods to incorporate fluorine into organic molecules, both from an academic and industrial perspective.[3]

In the past decades, transition metal mediated or catalyzed fluoroalkylation has emerged as a highly efficient alternative pathway to fluorination for the introduction of fluorine-containing structural motifs into organic molecules.[4] Among all methods developed, palladium-[5] and copper-catalyzed[6] fluoroalkylation reactions are undoubtedly the best known and reliable tools to afford fluoroalkylated motifs. Recently, nickel-catalyzed fluoroalkylation has attracted increasing attention because of the low cost and low toxicity of nickel catalysts, as well as broad substrate scope and excellent functional-group tolerance.[7] However, in all known examples thus far the coupling nucleophiles are limited to aryl, vinyl or alkyl metal species,[7a–h] and electron-rich (hetero)arenes,[7i,j] which clearly hampers the utility in organic synthesis (Scheme 1 a). As one part of our continuous efforts to develop nickel-catalyzed fluoroalkylations,[7d] we envisioned that a carboxylic acid, a versatile and readily available reagent widely used in metal-catalyzed decarboxylative cross-coupling reactions,[8] would be a desirable alternative to these coupling reagents. Meanwhile, to the best of our knowledge, there has been no report on nickel-catalyzed decarboxylative coupling of vinyl carboxylic acids without the help of a metal cocatalyst. Herein, we report the first example of a nickel-catalyzed decarboxylative difluoroalkylation of α,β-unsaturated carboxylic acids[9] with commonly available fluoroalkyl halides, in which high activity, excellent *E* selectivity, and broad substrate scope have been demonstrated (Scheme 1 b).



Scheme 1. Nickel-catalyzed fluoroalkylation. dppp = 1,3-bis(diphenylphosphino)propane, EWG = electron-withdrawing group.

Our initial investigation commenced with (*E*)-cinnamic acid [(*E*)-**1a**] as the substrate and ethyl iododifluoroacetate (**2**) as the fluoroalkyl coupling partner in the presence of a catalytic amount of $Ni(OAc)_2$ (10 mol %) in 1,4-dioxane at 70 °C (Table 1). While most of the ligands used in reported nickel-catalyzed fluoroalkylation systems, such as diamines and monophosphines, exhibited no catalytic reactivity (entries 1–4), to our delight, diphosphines afforded the desired difluoromethylated product **3a** successfully and dppp gave the best result with 85 % yield (entry 8). The ratio of nickel to diphosphorus ligand was next examined, and showed that 20 mol % of dppp (Ni/dppp = 1:2) still gave the best yield (entries 11–12). As the difluoroalkylated product was not formed in the absence of a base (entry 13), we surveyed a range of bases, including inorganic and organic bases, and found that NaOAc and KOAc were the optimal choices (entries 14–19). Solvent effects were also investigated, and indicated that the use of other solvents failed to improve yields (entries 20–23), and 1,4-dioxane still proved to be the best solvent. The control experiment showed that no difluoroalkylated product was observed in the absence of the nickel catalyst (entry 24).

With the optimized reaction conditions in hand, the scope with respect to the α,β-unsaturated carboxylic acids was examined (Table 2). While a series of *para*-substituted cinnamic acids bearing either electron-donating (**1b–g**) or electron-withdrawing (**1h–p**) functional groups gave high

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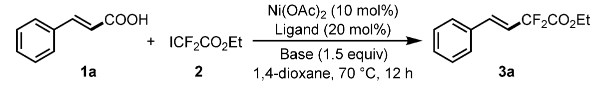
Table 1: Nickel-catalyzed decarboxylative difluoroalkylation: optimization of reaction conditions.[a]

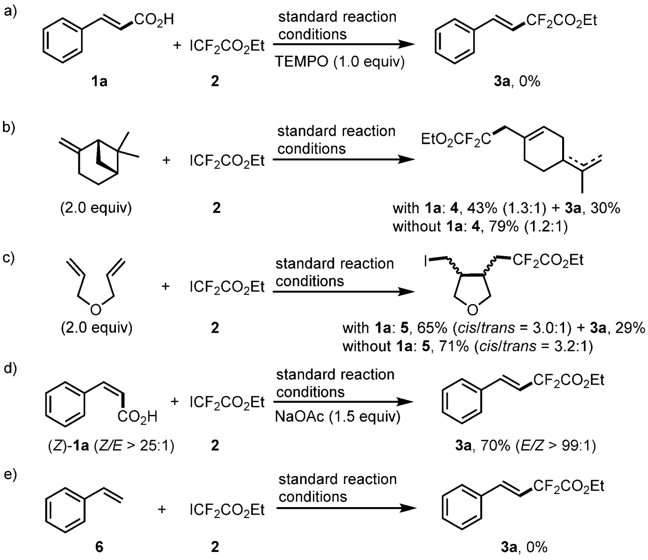


Entry	Base	Ligand	Yield [%][b]
1	KOAc	TMEDA	0
2	KOAc	DMEDA	0
3	KOAc	bpy	0
4	KOAc	PPh_3	0
5	KOAc	BINAP	10
6	KOAc	Xantphos	39
7	KOAc	dppe	trace
8	KOAc	dppp	85
9	KOAc	dppb	trace
10	KOAc	dppf	36
11[c]	KOAc	dppp	68
12[d]	KOAc	dppp	59
13	–	dppp	0
14	K_2CO_3	dppp	35
15	$KHCO_3$	dppp	71
16	K_3PO_4	dppp	70
17	NaOAc	dppp	78
18	Et_3N	dppp	61
19	DIPEA	dppp	66
20[e]	KOAc	dppp	52
21[f]	KOAc	dppp	46
22[g]	KOAc	dppp	70
23[h]	KOAc	dppp	39
24[i]	KOAc	dppp	0

[a] Unless noted otherwise, the reaction conditions were as follows: **1a** (0.4 mmol, 2.0 equiv), **2** (0.2 mmol, 1.0 equiv), 1,4-dioxane (2.0 mL), N_2. [b] Yield of isolated product. [c] Used dppp (15 mol%). [d] Used dppp (10 mol%). [e] Et_2O was used as the solvent. [f] THF was used as the solvent. [g] EtOAc was used as the solvent. [h] DCM was used as the solvent. [i] No $Ni(OAc)_2$. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, bipy = 4,4′-bipyridine, DIPEA = diisopropylethylamine, DMEDA = *N,N*′-dimethylethylenediamine, TMEDA = *N,N,N*′,*N*′-tetramethylethylenediamine, Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

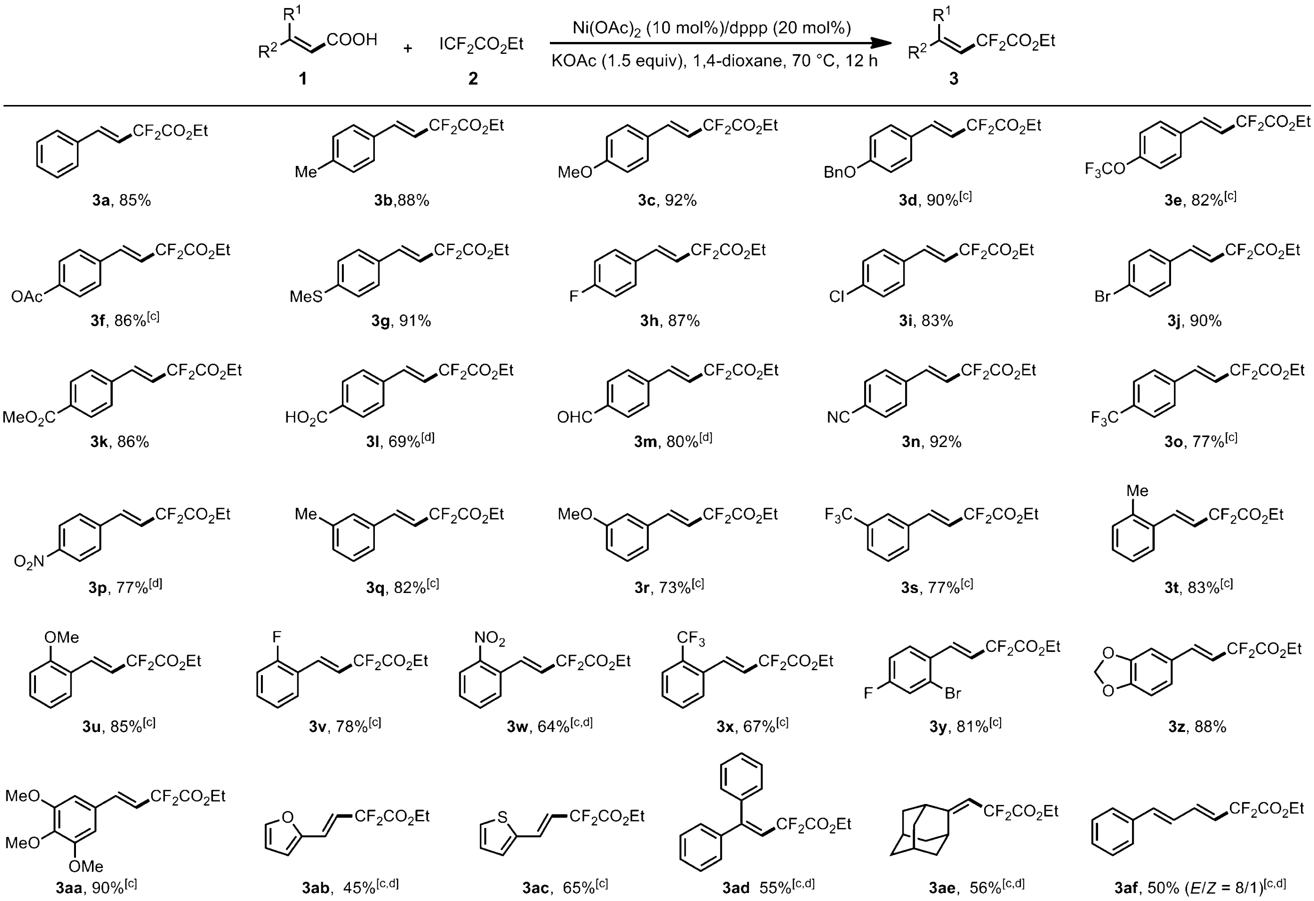
yields of the desired products in our new catalytic system, to our surprise, *ortho*- and *meta*-substituted cinnamic acids afforded only trace amounts of products when KOAc was used as base. To address this problem, a careful investigation of the base was performed with 3-methylcinnamic acid (**1q**) as the model substrate. Gratefully, the reaction proceeded smoothly with high yield by simply changing the base from KOAc to NaOAc (for details, see the Supporting Information). Fortunately, cinnamic acids with various *ortho*- and *meta*-substituted functional groups in the aryl rings were well tolerated, thus affording the corresponding fluoroalkylated products in moderate to high yields (**3q–x**). It was noteworthy that steric effect in this catalytic system could almost be ignored (**3t–y**, **3aa**). Interestingly, (*E*)-4-(2-carboxyvinyl)benzoic acid (**1l**), bearing two carboxylic groups, one connected to the alkene and one to the phenyl ring, was decarboxylated at vinyl position regiospecifically to give the difluoromethylated product **3l** as the sole product in 69% yield. Remarkably, decarboxylative difluoroalkylation of heteroarene-based acrylic acids could also proceed smoothly to afford the corresponding fluoroalkylated styrenes with moderate yields (**3ab–ac**). Intriguingly, only *E* isomers of difluoromethylated products were observed in all cases where (*E*)-**1a** or its derivatives were investigated, and thus demonstrated the excellent stereoselectivity of our newly developed catalytic system. Moreover, di- and trisubstituted α,β-unsaturated carboxylic acids (**1y–aa**) also afforded the desired products in good to high yields (81–90%), even for the alkyl-substituted vinyl carboxylic acid **1ae**. Finally, the (2*E*,4*E*)-5-phenylpenta-2,4-dienoic acid (**1af**) also underwent decarboxylative difluoromethylation smoothly with an acceptable yield, albeit with a slightly lower *E*/*Z* selectivity (8:1).

To gain some insight into the mechanism of this transformation, a series of control experiments were carried out (Scheme 2). Firstly, the reaction was completely quenched when 1.0 equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a common radical inhibitor, was added into the catalytic system and thus implied that this transformation may proceed by a radical pathway (Scheme 2a). To further verify this speculation, β-pinene and allyl ether, two known radical clocks, were used to trap the difluoromethyl radical. As we expected, $^{\bullet}CF_2CO_2Et$ was successfully captured by both reagents, thus giving the ring-opened diene **4** and cyclized ether **5** (Scheme 2b,c) in moderate yields under the standard reaction conditions with and without added **1a**. These results further confirmed the difluoromethyl radical was generated in situ in the catalytic system. Moreover, (*Z*)-**1a** also afforded the same *trans*-alkenes product **3a** as (*E*)-**1a** did, and additionally verified this stereoconvergent reaction proceeded by a radical pathway (Scheme 2d). To determine whether the difluoroalkylation took place before the decarboxylation or not, the styrene **6** was subjected to the reaction system in place of **1a**. However, the reaction failed to afford desired product **3a** (Scheme 2e), thus indicating that styrene



Scheme 2. Preliminary mechanistic studies.

Table 2: Nickel-catalyzed decarboxylative fluoroalkylation of α,β-unsaturated carboxylic acids.[a,b]



3a, 85%; **3b**, 88%; **3c**, 92%; **3d**, 90%[c]; **3e**, 82%[c]

3f, 86%[c]; **3g**, 91%; **3h**, 87%; **3i**, 83%; **3j**, 90%

3k, 86%; **3l**, 69%[d]; **3m**, 80%[d]; **3n**, 92%; **3o**, 77%[c]

3p, 77%[d]; **3q**, 82%[c]; **3r**, 73%[c]; **3s**, 77%[c]; **3t**, 83%[c]

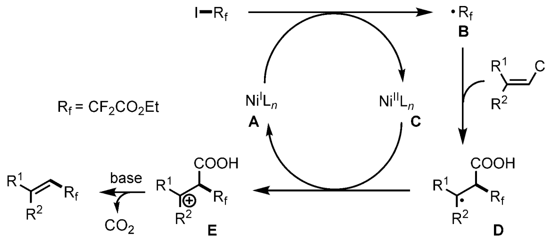
3u, 85%[c]; **3v**, 78%[c]; **3w**, 64%[c,d]; **3x**, 67%[c]; **3y**, 81%[c]; **3z**, 88%

3aa, 90%[c]; **3ab**, 45%[c,d]; **3ac**, 65%[c]; **3ad** 55%[c,d]; **3ae**, 56%[c,d]; **3af**, 50% (*E*/*Z* = 8/1)[c,d]

[a] Unless otherwise noted, the reaction conditions were as follows: (*E*)-**1a** (0.4 mmol, 2.0 equiv), **2** (0.2 mmol), Ni(OAc)$_2$ (10 mol%), dppp (20 mol%), KOAc (1.5 equiv), 1,4-dioxane (2 mL), 70 °C, 12 h, N$_2$. [b] Yield is that of the isolated product. [c] NaOAc was used instead of KOAc. [d] 100 °C.

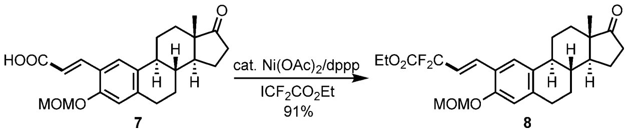
was not the intermediate and the decarboxylation occurred after the difluoromethylation step.

Based on the above results and previous reports,[10] a plausible mechanism for this nickel-catalyzed decarboxylative fluoroalkylation is proposed in Scheme 3. The catalytic cycle was initiated by the in situ generated nickel(I) species **A**, which could be oxidized by fluoroalkyl iodide (**2**) through a single-electron transfer to afford the fluoroalkyl radical **B** and nickel(II) species **C**. Subsequently, the fluoroalkyl radical **B** attacked the α-carbon atom of the vinyl carboxylic acid to afford the carbon radical **D**, which underwent oxidation with **C** to give the cationic intermediate **E**. Finally, the desired fluoroalkyl product was obtained by recovery of the double bond through an elimination of carbon dioxide with the help of base.



Scheme 3. Proposed mechanism.

To demonstrate the practical utility of this method, this catalytic system was applied to the late-stage fluoroalkylation of biologically active molecules. As shown in Scheme 4, the estrone derivative **7**, synthesized from estrone in three steps, underwent decarboxylative difluoromethylation to yield **8** in excellent yield (91%). This outcome demonstrates the great potential of this difluoromethylation method in drug discovery and development as it is a facile strategy for synthesis of fluoroalkylated analogues.



Scheme 4. Difluoroalkylation of the estrone derivative **7**.

In summary, we have developed the first nickel-catalyzed decarboxylative fluoroalkylation of α,β-unsaturated carboxylic acids. Compared with the known catalytic nickel system, this transformation demonstrates broad substrate scope, excellent functional-group tolerance, and mild reaction conditions. Mechanistic investigations revealed that a free difluoroalkyl radical was involved in the catalytic cycle. Further investigations of reaction mechanism and application of this method to modify the bioactive molecules, are underway in our laboratory.

Acknowledgments

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