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Palladium-Catalyzed Regioselective Difluoroalkylation and Carbonylation of Alkynes

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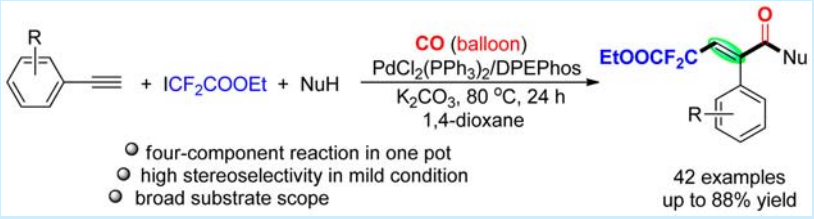
Supporting Information

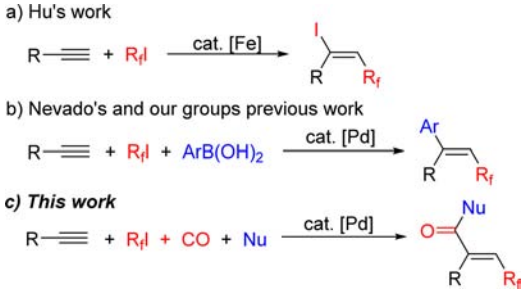


ABSTRACT: A novel, four-component synthetic strategy to synthesize a series of β-difluoroalkyl unsaturated esters/amides with high regioslectivity is described. This Pd-catalyzed difluoroalkylation and carbonylation reaction can be carried out with simple starting materials. Through this protocol, two new C−C bonds (including one C−CF_2 bond) and one C−O(N) bond are constructed simultaneously in a single step. The synthetic utility of this reaction system has been certified by the applicability to a wide scope of alkynes and nucleophiles. Preliminary mechanistic studies suggest that the difluoroalkyl radical pathway is involved in this reaction.

Introducing fluorine atoms into an organic molecule usually leads to dramatic improvement of the parent molecule in biological and physicochemical properties.[1] Typically, the difluoromethylene group (CF_2), which serves as a bioisostere for the oxygen atom or carbonyl group,[2] has significant applications in biologically active molecules.[3] Therefore, the advancing aspirations and continuous interests to explore new routes to introduce the CF_2 group stimulate further studies in organofluorine chemistry.[4] In recent years, new synthetic strategies for the synthesis of fuoroalkylated alkynes via alkyne difunctionalization process with high efficiency warrants further investigation.[5] In 2014, Hu and co-workers reported an iron-catalyzed reaction of alkynes with perfluoroalkyl iodides to afford β-fluoroalkyl vinyl iodides (Scheme 1a), which showed high reactivity and could be easily turned into other functionalized fluoroalkyl-containing groups.[6] In 2015, Nevado and our group demonstrated a palladium-catalyzed, three-component, intermolecular aryldifluoroalkylation of alkynes, respectively (Scheme 1b and 1c).[7,8] Despite this big step, the functional difluoroalylation by these reactions, a novel, efficient, and stereoselective idea to enrich the synthesis of CF_2-containing moieties is highly desirable. Meanwhile, answering questions about the "most convenient" and "most efficient" experimental procedures to achieve much more complex structures is still a challenge.

Transition-metal-catalyzed multicomponent reactions[9] proved to be a powerful tool in organic synthesis methodology due to high efficiency and atom economy, which could avoid tedious starting material preparations. Moreover, palladium as the catalyst provides the most direct avenues to construct carboxylic acids and their derivatives such as esters and amides in multicomponent carbonylation.[10] By taking into consideration our current interest in Pd-catalyzed multicomponent reactions and difunctionalized fluoroalkylation of alkynes, we proceeded to probe the possibility of intermolecular fluoroalkylation/carbonylation reactions with alkynes as the starting materials. Herein, we disclose a novel, Pd-catalyzed, four-component fluoroalkylation/carbonylation of alkynes with ethyl difluoroiodoacetate and a series of nucleophiles. Compared to traditional routes to RCONu, no preparations of alkenyl halides

Scheme 1. Synthesis of Functionalized Difluoroalkyl Compounds through Difunctionalization of Alkynes and Our New Anticipation



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were needed,[11] which alleviated time-consuming synthesis. In addition, from the point of synthetic efficiency, two new C−C bonds and one C−O(N) bond were constructed simultaneously in a single step.

According to the previous work,[12] our investigations, initially, started with phenylacetylene (**1a**) and MeOH (**2a**) as model substrates. The reaction was allowed to run with ethyl difluoroiodoacetate in the presence of $Pd(PPh_3)_4$ (5 mol %) and Cs_2CO_3 (1.0 equiv) at 80 °C under a CO atmosphere (balloon pressure) for 6 h. A better result of 23% yield was observed in 1,4-dioxane identified by GC (Table 1, entries 1−5).

Table 1. Optimization of the Reaction Conditions[a]

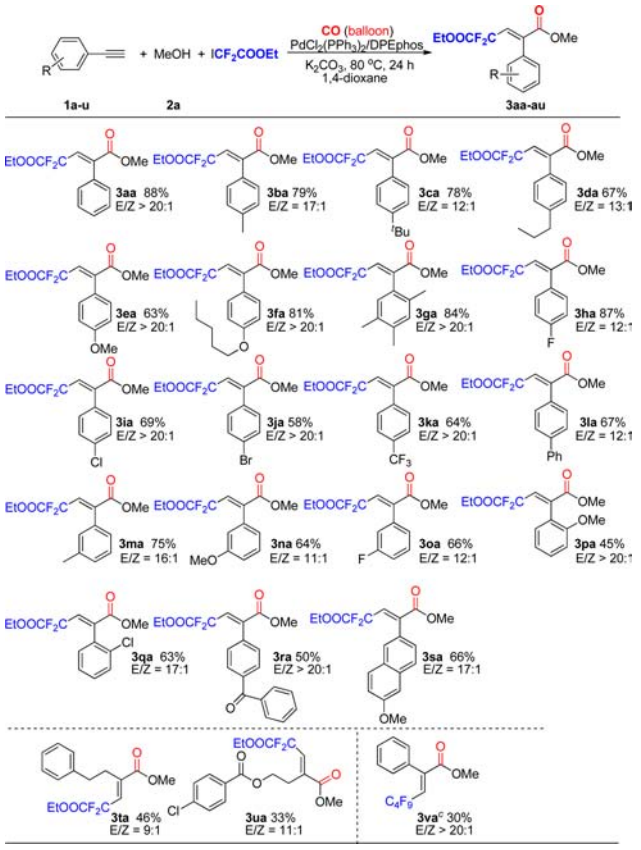
entry	catalyst (mol %)	base (equiv)	solvent	yield[b] (%)
1	$Pd(PPh_3)_4$ (5)	Cs_2CO_3 (1.0)	DMF	0
2	$Pd(PPh_3)_4$ (5)	Cs_2CO_3 (1.0)	toluene	20
3	$Pd(PPh_3)_4$ (5)	Cs_2CO_3 (1.0)	THF	19
4	$Pd(PPh_3)_4$ (5)	Cs_2CO_3 (1.0)	NMP	19
5	$Pd(PPh_3)_4$ (5)	Cs_2CO_3 (1.0)	1,4-dioxane	23
6	$Pd(PPh_3)_4$ (5)	K_2CO_3 (1.0)	1,4-dioxane	37
7	$Pd(PPh_3)_4$ (5)	K_2CO_3 (1.5)	1,4-dioxane	49
8[c]	$Pd(PPh_3)_4$ (20)	K_2CO_3 (1.5)	1,4-dioxane	78 (74)
9[c,d]	$Pd(OAc)_2$ (5)	K_2CO_3 (1.5)	1,4-dioxane	78
10[c,d]	**$PdCl_2(PPh_3)_2$ (5)**	**K_2CO_3 (1.5)**	**1,4-dioxane**	**91 (88)**
11[c,d]	$PdCl_2(MeCN)_2$ (5)	K_2CO_3 (1.5)	1,4-dioxane	83

[a]Unless otherwise noted, the reactions were performed: **1a** (0.20 mmol), **2a** (0.60 mmol), ethyl difluoroiodoacetate (0.34 mmol), catalyst (5 mol %), solvent (1.0 mL), CO (balloon), 6 h, 80 °C. [b]Determined by GC (phenylate was used as internal standard, and isolated yields were noted in parentheses). [c]This reaction was performed for 24 h. [d]DPEPhos (10 mol %) was added.

Then, the adjustment of base to K_2CO_3 (1.5 equiv) gave a moderate yield of 49% (Table 1, entries 6−7). Increasing the loading of $Pd(PPh_3)_4$ to 20% and prolonging the reaction time to 24 h led to a yield of 74% (Table 1, entry 8). Considering that this transformation heavily relied on such a high dosage of the Pd(0) catalyst, changing the Pd catalytic system may be a good option. In this regard, various Pd(II) (5 mol %)/ligand (10 mol %) complexes were screened, in which $PdCl_2(PPh_3)_2$/DPEPhos exhibited the best performance for this transformation, giving product **3aa** in an isolated yield of 88% (Table 1, entry 10). (For details, see the Supporting Information.)

With the established procedure in hand, the scope of the difunctionalization reaction was explored subsequently. First, a series of alkynes were investigated. This difluoroalkylation/carbonylation reaction displayed a high ability to bear alkynes with various substituents. As demonstrated in Scheme 2. Both electron-donating and -withdrawing substituents on the aromatic rings showed good compatibility to this reaction, and the corresponding products were obtained smoothly in good to excellent yields. The alkyne with 2,4,5-trimethyl substituents on the aromatic ring afforded the desired product **3ga** in a high yield of 84%. Even, ethynylnaphthalene participated efficiently in the difunctionalization reaction to provide the desired product **3sa** in 66% yield. It is worth mentioning that alkylalkynes also

Scheme 2. Substrate Scope on Alkynes[a,b]



[a]Reaction conditions: **1a−1u** (0.20 mmol), **2a** (0.60 mmol), ethyl difluoroiodoacetate (0.34 mmol), K_2CO_3 (0.30 mmol), catalyst (5 mol %), ligand (10 mol %), 1,4-dioxane (1.0 mL), CO (balloon), 24 h, 80 °C. Isolated yields. [b]The ratios of *E*/*Z* isomers were determined by ^{19}F NMR spectroscopy, and structures of the major isomers are shown. [c]IC_4F_9 was used instead of ICF_2COOEt.

underwent this difunctionalization process (**3ta** and **3ua**), despite the lower yields of the corresponding products that were obtained. Poor *E*/*Z* product ratios were obtained when the *m*-position was functionalized (**3ma−3oa**).

Next, numerous frequently used alcohols were investigated as nucleophiles (Scheme 3). Good results were obtained when MeOH and EtOH were used under the optimized reaction conditions. Allyl alcohol and *tert*-butanol failed to give the desired products, but satisfactory results were still obtained when primary and secondary alcohols were used. Importantly, several phenols also proved suitable for this transformation, which gave the corresponding products in moderate yields (**4aj−4am**).

Finally, miscellaneous amines were also tested to broaden the substrate scale under the optimized conditions (Scheme 4). Monosubstituted aryl amines (**4an−4aq**) were tolerated in this transformation as well as alkyl amines (**4ar** and **4as**) with excellent *E*/*Z* product ratios obtained. Adding cyclohexylamine or piperidine to the standard reaction conditions resulted in the formation of ester−amide exchanged products (**4at** and **4au**),[13] in which two C−C bonds and two C−N bonds were formed. Furthermore, the X-ray crystal structure of the major isomer **4au** was also confirmed (for details, see the Supporting Information). However, similar to the situation with an allyl alcohol, the result of allylamine proceeded unsatisfactorily (**4av**).

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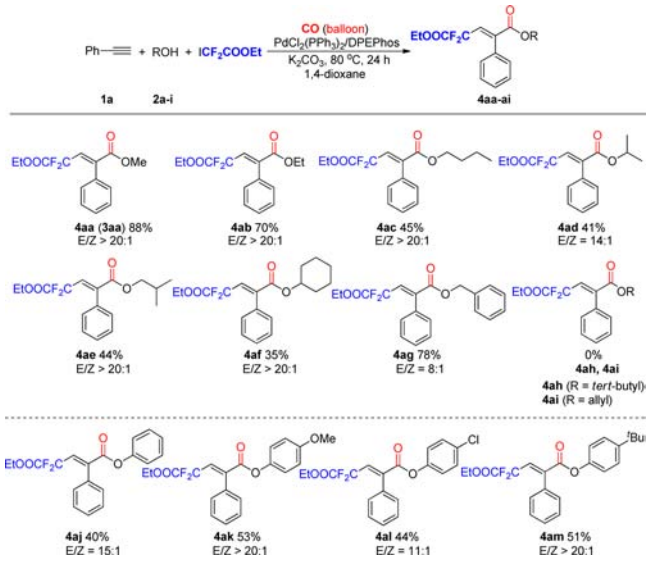
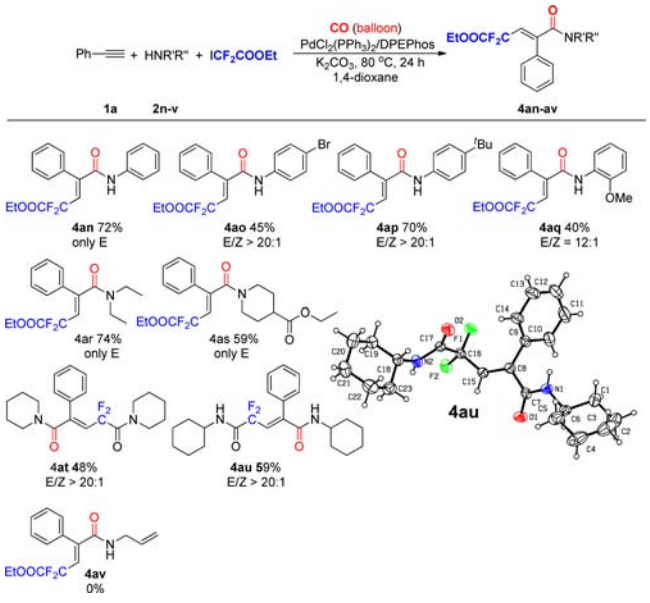
Scheme 3. Substrate Scope on Alcohols and Phenols[a,b]



[a]Reaction conditions: **1a** (0.20 mmol), **2a**−**2i** (0.60 mmol), ethyl difluoroiodoacetate (0.34 mmol), K_2CO_3 (0.30 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), DPEPhos (10 mol %), 1,4-dioxane (1.0 mL), CO (balloon), 24 h, 80 °C. Isolated yields. [b]The ratios of *E*/*Z* isomers were determined by ^{19}F NMR spectroscopy, and structures of the major isomers are shown.

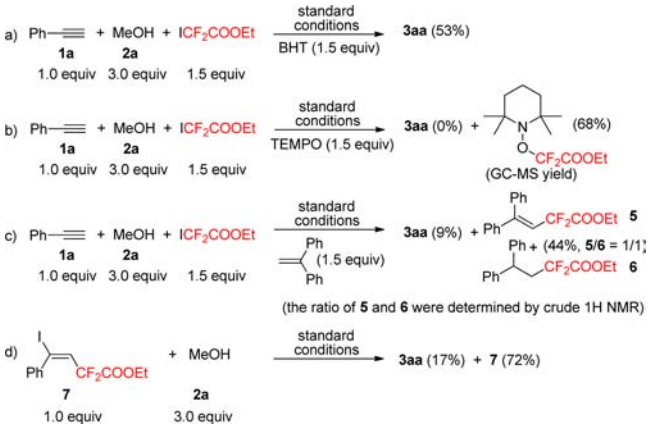
Scheme 4. Reaction Scope on Amines[a,b]



[a]Reaction conditions: **1a** (0.20 mmol), **2n**−**2v** (0.60 mmol), ethyl difluoroiodoacetate (0.34 mmol), K_2CO_3 (0.30 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), DPEPhos (10 mol %), 1,4-dioxane (1.0 mL), CO (balloon), 24 h, 80 °C. Isolated yields. [b]The ratios of *E*/*Z* isomers were determined by ^{19}F NMR spectroscopy, and structures of the major isomers are shown.

To understand the reaction pathway better, several control experiments were performed. When BHT, TEMPO, or 1,1-diphenylethylene was added into the reaction mixtures under the standard conditions, respectively, the product **3aa** declined sharply. Meanwhile, 68% of the TEMPO−CF_2COOEt adduct was detected (Scheme 5b) and 44% of a mixture of **5** and **6** was obtained (Scheme 5c). As a consequence of the above-mentioned

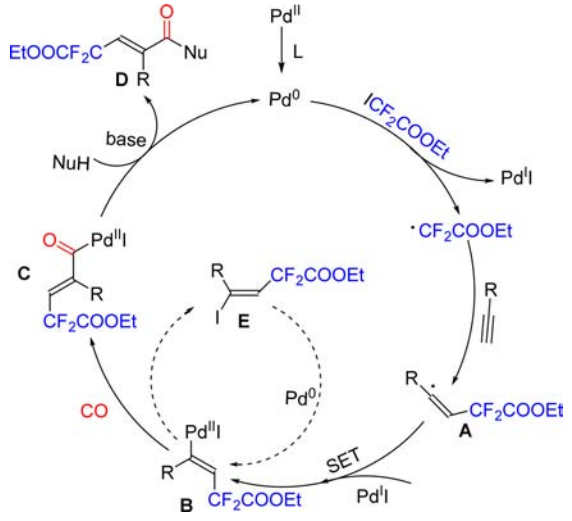
Scheme 5. Control Experiments



experimental results, a difluoroalkyl radical addition pathway was suggested in the process.[6−8] To assess whether vinyl iodides (as side products, observed in the reaction systems) played a significant role in this transformation, another control experiment was performed (Scheme 5d). A small quantity of **4aa** (17%) was isolated, and 72% of **7** was recycled, indicating that vinyl iodides may be involved in this reaction pathway.

By combining the current relevant results reported,[14] as shown in Scheme 6, a plausible carbonylative mechanism with a

Scheme 6. Plausible Mechanism



difluoroalkyl radical is proposed. First, the difluoroalkyl radical is generated in the presence of Pd(0) (formed via ligand exchange). Then, the addition of the difluoroalkyl radical onto phenylacetylene gives the vinyl radical intermediate **A**. Subsequent recombination with Pd(I)I generates the key Pd(II) intermediate **B**. Finally, the insertion of carbon monoxide into the Pd(II) species **B** furnishes the intermediate **C**, which undergoes reductive elimination (in the presence of the nucleophile and base) to give the corresponding carbonylated alkenes **D** and regenerates Pd(0). In addition, reductive elimination of the Pd(II) species **B** also affords the side product vinyl iodide **E**, which could transform into the corresponding carbonylated alkenes **D** in 17% yield under the standard conditions.

In summary, we have reported a Pd-catalzed four-component radical carbonylation and difluoroalkylation reaction utilizing ethyl difluoroiodoacetate as the CF_2 radical precursor under a

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balloon pressure of CO in a single step. Through this protocol, two new C−C bonds and one C−O(N) bond were constructed with high regioselectivity. The practical synthetic significance of this reaction system has been demonstrated by a wide spectrum of alkynes and nucleophiles. Moreover, the newly formed functional groups can be further derivatized by nucleophilic reactions etc. Also, this multicomponent reaction carried out with simple and readily available starting materials avoided the cumbersome multistep synthesis of raw materials. Further extension of this chemistry toward other nucleophiles is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01038.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

X-ray data for **4au** (CIF)

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Notes

The authors declare no competing financial interest.

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