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Palladium-Catalyzed Radical Cascade Iododifluoromethylation/Cyclization of 1,6-Enynes with Ethyl Difluoroiodoacetate

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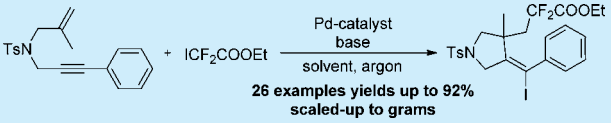
Supporting Information

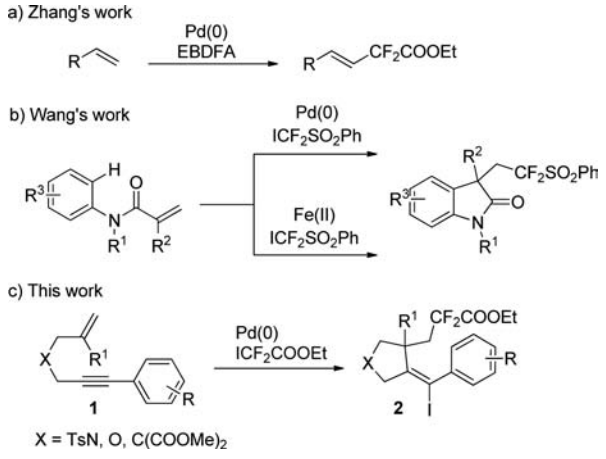
ABSTRACT: A novel and convenient Pd-catalyzed radical cascade iododifluoromethylation/cyclization of 1,6-enynes with ethyl difluoroiodoacetate is demonstrated. The proposed transformation presents high stereoselectivity under mild and facile reaction conditions, thereby allowing an efficient access to a variety of iodine-containing difluoromethylated pyrrolidines. A possible radical pathway for the transformation is proposed on the basis of the results of control experiments and relevant literature reviews.



Introducing fluoroalkyl groups into organic molecules often significantly changes the physical and biological properties of the resultant molecules and greatly improves their lipophilicity, metabolic stability, and bioavailability.[1] Thus, fluorine-containing compounds have gained ground in the fields of agrochemical and pharmaceutical production as well as materials science.[2] In particular, the difluoromethylene group (CF_2), which acts as a bioisostere for mimicking the electronic features of an ethereal oxygen atom as well as a lipophilic hydrogen-bond donor, has been regarded as a potential structural motif because of its unique properties.[3] Traditional strategies for synthesizing difluoroalkylated compounds often involve deoxofluorination of aldehydes or ketones with (diethylamino)sulfur trifluoride (DAST) or Deoxofluor.[4] Over the past few decades, several methods for incorporating the difluoromethylene group (CF_2) into organic molecules by transition-metal-catalyzed as well as free-radical-mediated difluoromethylation reactions have been developed.[5] For instance, the Hartwig[6] and Prakash[7] groups independently reported the copper-mediated nucleophilic difluoromethylation of aryl iodides with $TMSCF_2H$ and n-Bu_3SnCF_2H. Amii and co-workers described a sequential three-step copper-catalyzed approach (including cross-coupling, hydrolysis, and decarboxylation) to synthesize difluoromethyl aromatic and heteroaromatic compounds.[8] Baran developed convenient difluoromethylations of heterocycles with the use of zinc difluoromethanesulfinates (DFMS).[9] Recently, a range of intriguing researching studies have reported the construction of difluoromethyl-containing compounds through a radical addition process of alkenes. In 2012, Liu and co-workers described an iron-catalyzed decarboxylative difluoromethylation of cinnamic acids with zinc difluoromethanesulfinates (DFMS).[10] In 2014, Zhang developed a palladium-catalyzed radical fluoroalkylation of alkenes with fluoroalkyl bromides (Scheme 1a).[11] Wang reported palladium or iron-catalyzed radical aryldifluoromethylation/cyclization of various *N*-arylacrylamides to form useful difluoromethylated oxindole derivatives (Scheme 1b).[12]

Very recently, the Cho and Zhu groups reported visible light photoredox-catalyzed radical difluoroalkylations of alkenes and allylic alcohols with ethyl bromodifluoroacetate (EBDFA) as the difluoromethyl source, respectively.[13] Despite the obvious benefits of the aforementioned difluoromethylation strategies, a concise, moderate, and economical difluoromethylation strategy for synthesizing complex organic compounds remains highly desired.

Scheme 1. Summary of the Present Research and Our New Transformation of Iododifluoromethylation/Cyclization of 1,6-Enynes



As a series of good radical receptors, 1,6-enynes have been considered as valuable and versatile scaffolds in medical and biological chemistry and may be used to establish efficient methods to construct pyrrolidines and other five-membered heterocycles.[14] The tandem cyclization of 1,6-enynes to incorporate two important functional groups has gained increased interest because of the aforementioned advantages.[15] In particular, iodine atoms, which occur in large amounts of organic intermediates and natural products, can be widely used for cross-coupling reactions and nucleophilic substitutions.

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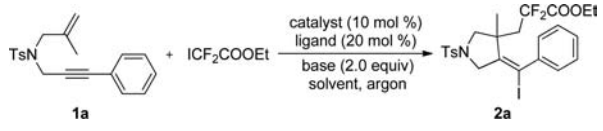
Notably, chemists have exerted efforts to develop different strategies to introduce iodine and fluorinated groups in one step.[16] Recently, our group disclosed several radical cyclization reactions of 1,6-enynes for the synthesis of trifluoromethyl/nitro substituted heterocycles and phosphorated fluorine derivatives.[15a,b,17] The synthesis of iodine/difluoromethylene-containing pyrrolidines via a radical addition pathway has never been explored. Therefore, the goal of the present work is to establish a safe and green strategy for introducing iodine and difluoromethylene groups to 1,6-enynes. With previous studies as bases and with the 1,6-enyne substrates as our focus, herein we report in this paper the palladium-catalyzed radical-mediated iododifluoromethylation/cyclization of 1,6-enynes to yield iodine/difluoromethylene substituted pyrrolidines and other five-membered heterocycle derivatives (Scheme 1c).

Initially, our investigation was carried out by employing 1,6-enyne **1a** as the pilot substrate with the commercially available reagent ethyl difluoroiodoacetate (2.0 equiv) as difluoromethyl source, in the presence of $PdCl_2(MeCN)_2$ (10 mol %), DPE-Phos (20 mol %), and K_2CO_3 in dioxane (2.0 mL) at 25 °C under an argon atmosphere. Gratifyingly, our expected product **2a** was isolated in 43% yield after 10 h (Table 1, entry 1). Meanwhile the

Table 1. Optimization of Reaction Conditions[a]



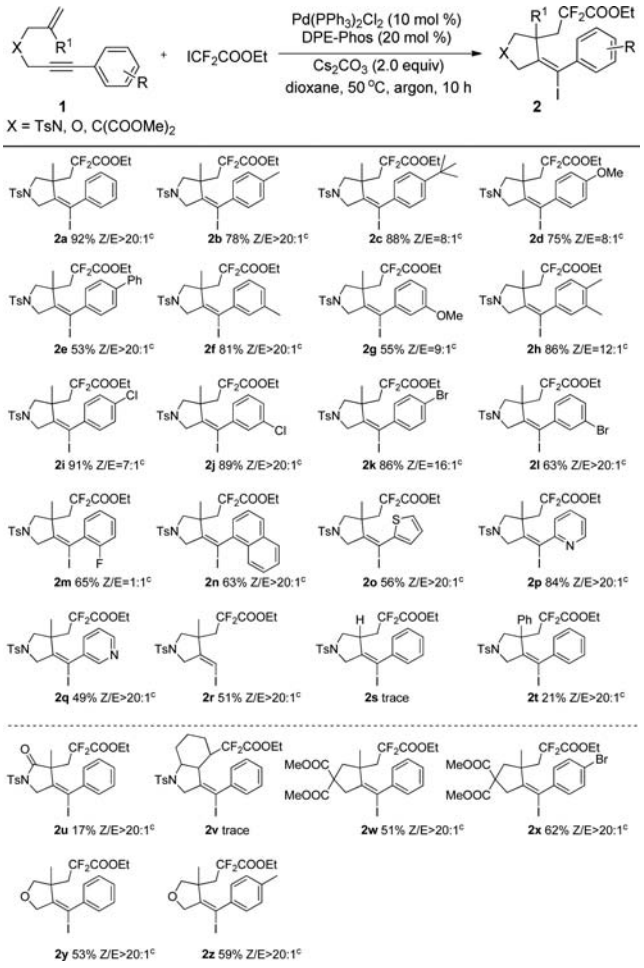
entry	[Pd] (mol %)	ligand (mol %)	base (equiv)	yield[b] (%)
1	$PdCl_2(MeCN)_2$ (10)	DPE-Phos (20)	K_2CO_3 (2.0)	43
2	$Pd(dba)_2$ (10)	DPE-Phos (20)	K_2CO_3 (2.0)	32
3	$Pd(OAc)_2$ (10)	DPE-Phos (20)	K_2CO_3 (2.0)	37
4	$PdCl_2(PPh_3)_2$ (10)	DPE-Phos (20)	K_2CO_3 (2.0)	46
5	$PdCl_2(PPh_3)_2$ (10)	PPh_3 (20)	K_2CO_3 (2.0)	N.R.
6	$PdCl_2(PPh_3)_2$ (10)	dppb (20)	K_2CO_3 (2.0)	trace
7	$PdCl_2(PPh_3)_2$ (10)	X-Phos (20)	K_2CO_3 (2.0)	33
8	$PdCl_2(PPh_3)_2$ (10)	XantPhos (20)	K_2CO_3 (2.0)	39
9	$PdCl_2(PPh_3)_2$ (10)	DPE-Phos (20)	Na_2CO_3 (2.0)	trace
10	$PdCl_2(PPh_3)_2$ (10)	DPE-Phos (20)	KOAc (2.0)	64
11	$PdCl_2(PPh_3)_2$ (10)	DPE-Phos (20)	K_3PO_4 (2.0)	66
12	$PdCl_2(PPh_3)_2$ (10)	DPE-Phos (20)	Cs_2CO_3 (2.0)	73
13[c]	**$PdCl_2(PPh_3)_2$ (10)**	**DPE-Phos (20)**	**Cs_2CO_3 (2.0)**	**92**
14	$PdCl_2(PPh_3)_2$ (0)	DPE-Phos (0)	Cs_2CO_3 (2.0)	N.R.

[a]Reaction conditions: **1a** (0.2 mmol), ethyl difluoroiodoacetate (2.0 equiv) in anhydrous dioxane (2.0 mL) under an argon atmosphere at 25 °C for 10 h. [b]Isolated yields. [c]At 50 °C.

molecular structure of **2a** was unambiguously determined by X-ray crystallographic analysis (see the Supporting Information). Inspired by this result, different palladium catalysts were varied for this transformation. Among the catalysts surveyed, we found that $PdCl_2(PPh_3)_2$ was the most efficient, promoting an increasing yield to 46% (Table 1, entries 1−4). In contrast to DPE-Phos, other ligands including diphosphines and monophosphines failed to show more catalytic reactivity (Table 1, entries 5−8). A subsequent survey on several representative bases indicated that Cs_2CO_3 was the most suitable catalyst, producing product **2a** in 73% yield (Table 1, entries 9−12). To improve the yield further, various solvents were examined, and dioxane exhibited the best performance for the reaction. The adjustments in reaction temperature revealed that this transformation reached the highest reaction activity of the desired product **2a** (92%) at 50 °C (Table 1, entry 13). Additionally, no product was formed without palladium catalyst or ligand (Table 1, entry 14). Finally, the use of **1a** (1.0 equiv), $PdCl_2(PPh_3)_2$ (10 mol %), DPE-Phos (20 mol %), and Cs_2CO_3 (2.0 equiv) with ethyl difluoroiodoacetate (2.0 equiv) in the presence of dioxane (2.0 mL) under an argon atmosphere at 50 °C for 10 h was considered the optimal reaction conditions.

With the optimized reaction conditions in hand (Table 1, entry 13), the substrate scope of 1,6-enynes was then tested. As depicted in Scheme 2, 1,6-enynes with both electron-donating

Scheme 2. Substrate Scope of the Iododifluoromethylation/Cyclization of 1,6-Enynes[a,b]



[a]All of the reactions were carried out in the presence of **1** (0.2 mmol), $PdCl_2(PPh_3)_2$ (10 mol %), DPE-Phos (20 mol %), ethyl difluoroiodoacetate (2.0 equiv), and Cs_2CO_3 (2.0 equiv) in dioxane (2.0 mL) under an argon atmosphere at 50 °C for 10 h. [b]Isolated yields. [c]The ratios of *Z*/*E* isomers were determined by ^{19}F NMR spectroscopy. Structures of the major isomers are shown.

and electron-withdrawing groups on the phenyl ring (**1a−m**) were well tolerated in this protocol and furnished excellent yields of the corresponding iododifluoromethylated pyrrolidines (**2a−m**) with good stereoselectivities and no evident electronic effect. In most cases, excellent *Z*/*E* product ratios were obtained. It is noteworthy that when the *ortho*-position was substituted, the reaction occurred smoothly to undergo an iododifluoromethylation/cyclization process with low stereoselective ratios of *Z*/*E*

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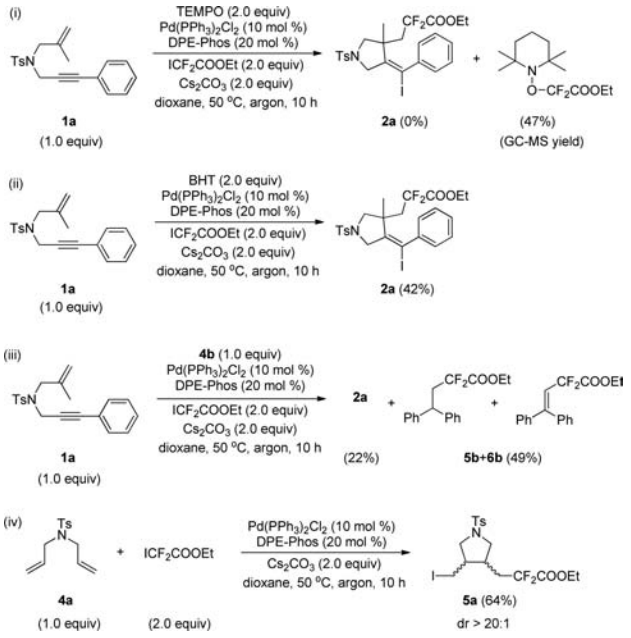
isomer. Considering this phenomenon, a hypothesis on the significant effect of steric hindrance influenced on the stereoselectivity is proposed. The reaction occurred mildly when 2-naphthalenyl was attached to the triple bond **1n**. In addition, a series of heterocyclic groups or no group attached to the triple bond (**1o**−**r**) were compatible with the reaction conditions, resulting in good yields and stereoselectivities. When unsubstituted allylic substrate **1s** and enyne **1v** were applied under the standard conditions, only trace amounts of **2s** and **2v** were detected, whereas enyne with a phenyl substituent **1t** afforded the product **2t** in a decreased yield of 21%. Based on these cases, we indicated that the substituents in the internal position of the alkene affected the stereoselectivity dramatically. After subsequent investigation of the scope of this reaction, we found that the carbon-tethered (**1w**, **1x**) and oxygen-tethered (**1y**, **1z**) 1,6-enynes as well as methacrylamide (**1u**) could also be converted into the desired products in moderate yields. Finally, the molecular structures of **2m** and **2p** were unambiguously confirmed through X-ray crystallography (see the Supporting Information for data for **2m** and 2p).

To gain insight into the mechanism of this reaction, a series of mechanistic studies were performed (Scheme 3). When 2.0 equiv

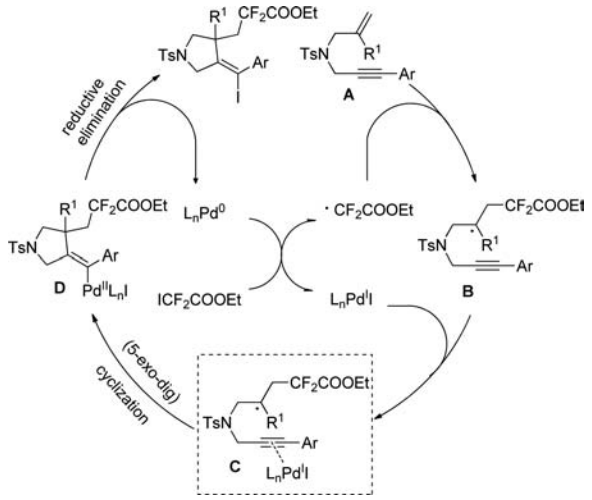
Scheme 3. Control Experiments for Mechanistic Studies



of TEMPO (2,2,6,6-tetramethylpiperidinyloxy, a well-known radical scavenger) were added to the reaction system, no product was detected, and the TEMPO−CF_2COOEt adduct was observed by GC−MS with a yield of 47%. BHT (2,6-di-*tert*-butyl-4-methyl-phenol), a radical inhibitor, was used under the standard conditions for the reaction, and the resultant difluoroalkylated product **2a** was isolated with low yield (42%). The yield of product **2a** decreased by 22% when a stoichiometric amount of ethene-1,1-diyldibenzene (**4b**) was added as a radical scavenger, and the **5b**−**6b** mixture was obtained in 49% yield. In addition, the reaction of *N*,*N*-diallyl-4-methylbenzenesulfonamide **4a** with ethyl difluoroiodoacetate under the standard reaction conditions resulted in the cyclized product **5a** with a yield of 64% (dr >20:1). The control experiments above demonstrated the involvement of the difluoromethyl radical in this process.

On the basis of the experimental results and previous literature, a plausible mechanism involving the difluoromethyl radical pathway was proposed (Scheme 4). First, ethyl

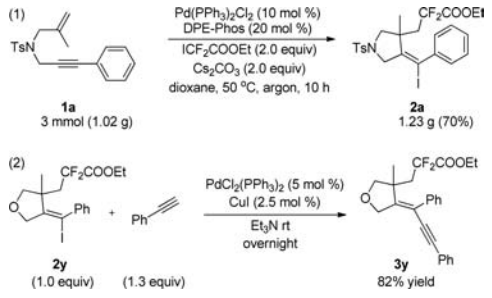
Scheme 4. Possible Mechanism



difluoroiodoacetate is reduced by Pd(0) to afford the CF_2 radical and Pd(I). The addition of the CF_2 radical to the double bond of 1,6-enyne **A** generates the radical intermediate **B**, which can be subsequently activated by Pd(I) to form **C**, and then an intramolecular 5-*exo-dig* cyclization follows to produce the Pd(II) iodine complex **D**. Finally, **D** undergoes reductive elimination to afford the final product and to regenerate the catalyst Pd(0).

In order to further evaluate the practicability of this method, the reaction of enynes **1a** and ethyl difluoroiodoacetates was enlarged to a gram scale under the optimal conditions, and the desired product **2a** was obtained in 70% yield (eq 1 in Scheme 5).

Scheme 5. Gram-Scale Experiment and Palladium-Catalyzed Coupling Reaction



Moreover, iododifluoromethylated product **2y** can be further elaborated by using the Sonogashira reaction.[18] The Sonogashira coupling of **2y** afforded the corresponding product **3y** in 82% yield (eq 2 in Scheme 5).

In conclusion, we have developed a palladium-catalyzed radical cascade iododifluoromethylation/cyclization of 1,6-enynes. This reaction provides an efficient protocol for preparing a variety of useful iododifluoromethylated pyrrolidines that may be used as potential intermediates in organic synthesis and medicinal chemistry. Compared with traditional difluoromethylation methods, our reaction system simultaneously introduces the pharmaceutically active group (CF_2) and takes advantage of the well-known cross-coupling utility of iodine. The mechanistic

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studies indicate that free-radical processes are involved in this system. Further research on the application of this reaction is currently underway 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.5b02068.

Detailed experimental procedures and spectral data for all new compounds (PDF)
Crystallographic data for **2a** (CIF)
Crystallographic data for **2m** (CIF)
Crystallographic data for **2p** (CIF)

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Notes

The authors declare no competing financial interest.

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