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Selective Mono- and Dialkynylation of 1-Fluoro-2,2-diiodovinylarenes Using Pd-Catalyzed Decarboxylative Coupling Reactions

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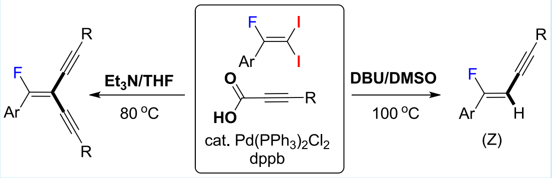
Supporting Information

ABSTRACT: Palladium-catalyzed decarboxylative coupling reactions using alkynoic acids and 1-fluoro-2,2-diiodovinylarenes provide mono- and dialkynylfluoroalkenes with high selectivity. When the reaction was conducted using DBU/DMSO, the hydrodeiodinated monoalkynylfluoroalkene product was formed, whereas performing the reaction using Et_3N/THF gave the dialkynylfluoroalkene product. Both reaction conditions gave high yields of the desired enyne and endiyne products bearing fluorine atoms.



The replacement of a hydrogen atom with fluorine at a specific site in a molecule has received a significant amount of attention because the resulting fluorinated compounds exhibit specific physicochemical properties. Fluorinated organic molecules have been widely employed in medicinal chemistry due to the unique properties of fluorine atoms, which can enhance their lipophilicity, bioavailability, and metabolic stability.[1] Among them, the vinyl fluoride moiety has been of great interest to our research group because it has been found in several bioactive molecules.[2] A number of synthetic methods used to prepare fluoroalkene derivatives have been developed and previously reported.[3] Among them, the hydrofluorination of alkynes was reported in a pioneering study and has been widely used.[4] A large amount of attention has been focused on developing this synthetic method for the preparation of useful fluoroalkene building blocks, which can be readily functionalized.

The enyne moiety has been found to be a crucial core structure in several biologically active molecules, such as antibacterial and anticancer reagents, and it is an important structure in biosensor molecules.[5] In addition, the endiyne moiety is a key component in conjugated molecules, acting as the fluorophore and chromophore.[6] However, general methods for the introduction of a vinyl fluoride moiety to enyne or endiyne structures have been less explored.[7] 1-Bromo-2-fluoro-2-arylethenes have been employed in the Sonogashira coupling reaction toward the synthesis of fluoro enynes.[8] However, this method requires the starting material to be prepared in a separate step.[9]

Decarboxylative coupling reactions using alkynoic acids have been studied by our group since our first report in 2008.[10] In particular, aryl-substituted alkynoic acids are widely used in transition-metal-catalyzed decarboxylative coupling reactions because they are readily prepared in one step upon reaction of an aryl halide and propiolic acid, without the need for purification by column chromatography.[11] A variety of coupling partners have been employed for the decarboxylative coupling reaction using aryl-substituted alkynoic acids with their corresponding alkynyl-substituted products formed in good yield.[12]

In addition, we have also developed a decarboxylative halogenation reaction of alkynoic acids.[13] Very recently, we reported that 1-fluoro-2,2-diiodovinylarenes can be obtained upon reacting alkynoic acid with Py·HF and 1,3-diiodo-5,5-dimethylhydantoin (DIH) in the presence of a catalytic amount of AgOAc.[14] 1-Fluoro-2,2-diiodovinylarenes are *gem*-diiodo-substituted alkenes that can react with a variety of nucleophiles via transition-metal-catalyzed coupling reactions. With this concept, we have already shown that the monocoupling product can be formed in the Hiyama reaction, and the dicoupling product was formed in the Suzuki coupling reaction. During our studies on the Pd-catalyzed coupling reactions of 1-fluoro-2,2-diiodovinylarenes, we found that the base is a very important factor that can control the mono- and dicoupling reaction.

A number of Sonogashira coupling reactions of *gem*-dihaloalkenes have been reported and used to prepare monoalkynyl- and dialkynylalkenes. Although *gem*-dibromoalkenes are frequently used in the synthesis of *gem*-dialkynylalkenes, they have some drawbacks including the formation of the monoalkynyl alkyne as a minor product.[15] However, to the best of our knowledge, *gem*-diiodoalkenes have never been used as coupling partners in either the Sonogashira or decarboxylative coupling reactions. Herein, we report the selective synthesis of monoalkynyl- and dialkynylfluoroalkenes via the decarboxylative coupling reaction of alkynoic acids and 1-fluoro-2,2-diiodovinylarenes. This is the first report of the coupling reaction between a *gem*-diiodoalkene and an *sp*-hybridized carbon atom.

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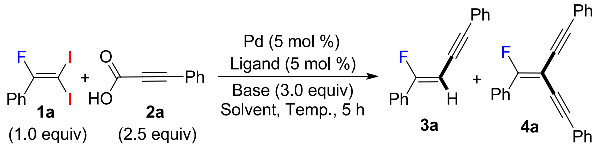
To obtain the optimal conditions for the decarboxylative coupling reaction, compound **1a** was allowed to react with phenylpropiolic acid under various conditions as a model reaction. The results are summarized in Table 1.

Table 1. Optimal Conditions for the Decarboxylative Coupling Reaction between 1a and 2a[a]



entry	ligand[b]	base	solvent	temp (°C)	yield[c] (%) 3a	yield[c] (%) 4a
1	**L1**	DBU	DMSO	100	92	0
2	**L2**	DBU	DMSO	100	87	0
3	**L3**	DBU	DMSO	100	70	0
4	**L4**	DBU	DMSO	100	79	0
5	**L1**	Et_3N	DMSO	100	22	0
6	**L1**	pyridine	DMSO	100	29	0
7	**L1**	DABCO	DMSO	100	16	0
8	**L1**	TBAF	DMSO	100	42	0
9	**L1**	Cs_2CO_3	DMSO	100	0	0
10	**L1**	DBU	diglyme	100	12	0
11	**L1**	DBU	xylene	100	67	0
12	**L1**	DBU	NMP	100	83	0
13	**L1**	DBU	THF	80	75	0
14[d]	**L1**	DBU	DMSO	100	60	0
15[e]	**L1**	DBU	DMSO	100	19	0
16[f]	**L1**	Et_3N	DMSO	80	65	trace
17[f]	**L1**	Et_3N	xylene	80	0	5
18[f]	**L1**	Et_3N	diglyme	80	0	22
19[f]	**L1**	Et_3N	THF	80	4	82
20[f]	**L1**	DIPEA	THF	80	8	0
21[f]	**L1**	TBAF	THF	80	5	0
22[f]	**L1**	DABCO	THF	80	10	27
23[g]	**L1**	Et_3N	THF	80	15	42
24[f]	**L1**	Et_3N	THF	50	21	0
25[f]	**L1**	Et_3N	THF	25	0	0
26[h]	**L1**	DBU	DMSO	100	91	0
27[f,h]	**L1**	Et_3N	THF	80	0	32

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.75 mmol), $Pd(PPh_3)_2Cl_2$ (0.015 mmol), ligand (0.015 mmol), and base (0.9 mmol) were reacted in the specified solvent (1.0 mL) at the temperature stated for 5 h. [b] **L1** = 1,4-bis(diphenylphosphino)butane, **L2** = 1,3-bis(diphenylphosphino)propane, **L3** = 1,2-bis(diphenylphosphino)benzene, **L4** = 1,1′-bis(diphenylphosphino)ferrocene. [c] Determined using ^1H NMR spectroscopy and gas chromatography with an internal standard. [d] 2.0 equiv of **2a** was used. [e] 1.0 equiv of **2a** was used. [f] Base (0.5 mL) and solvent (0.5 mL) were used in a 1:1 ratio. [g] 1.0 equiv of base was used. [h] Pd (0.0075 mmol) and **L1**(0.0075 mmol) were used.

Several ligands were studied in the presence of DBU and DMSO (entries 1–4). Surprisingly, the hydrodeiodination product (**3a**) was formed as the only product in good yield. No dicoupled product (**4a**) was observed even though 2.5 equiv of **2a** was employed in the reaction. Among them, **L1** afforded **3a** in 92% yield (entry 1). When other bases such as Et_3N, pyridine, DABCO, TBAF, and Cs_2CO_3 were employed instead of DBU, the reaction showed poor yield or no reaction (entries 5–9). Changing the solvent to diglyme gave **3a** in very poor yield (entry 10). Other solvents such as xylene, NMP, and THF provided **3a** in 67, 83, and 75% yield, respectively (entries 11–13). When the amount of phenylpropiolic acid was decreased to 2.0 and 1.0 equiv, the yield of **3a** decreased to 60 and 19%, respectively (entries 14 and 15). To obtain the dialkynylated product, an excess of base was employed. A mixture of Et_3N and DMSO provided **3a** as the major product (entry 16). When diglyme or xylene was employed as the reaction solvent in the presence of an excess amount of Et_3N, product **4a** was formed in 5 and 22% yield, respectively (entries 17 and 18). Using THF as the reaction solvent provided **4a** as the major product in 82% yield (entry 19). However, the reaction using other bases such as DIPEA and TBAF provided **3a** in very low yield (entries 20 and 21). When DABCO was used, a mixture of **3a** and **4a** was formed in 10 and 27% yield, respectively (entry 22). Decreasing the amount of Et_3N to 1.0 equiv resulted in a low yield with poor selectivity (entry 23). When the reaction was conducted at 50 or 25 °C, no dialkynylated product was found in both cases (entries 24 and 25). When the amount of palladium and ligand was decreased to 2.5 mol %, the yield of **3a** was not changed (entry 26); however, the yield of **4a** decreased to 32% (entry 27). It is noteworthy that the monocoupled product bearing a vinyl iodide group was not observed in all cases. Finally, we found that the reaction performed using DBU (3.0 equiv) and DMSO afforded the monoalkynyl product and the reaction carried out using Et_3N and THF gave the dialkynylated product.

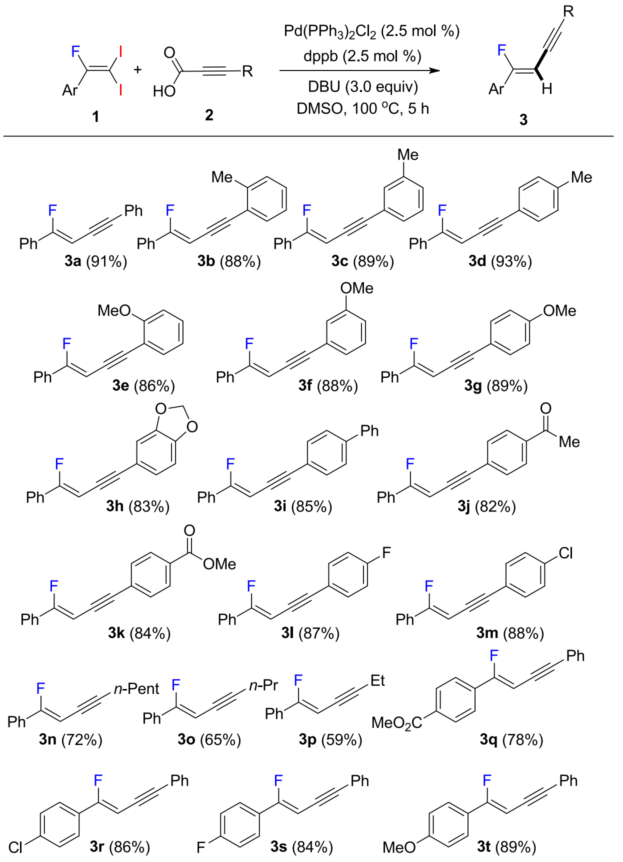
Using the optimal conditions for the monoalkynylation reaction, a variety of arylpropiolic acids were employed in the coupling reaction with several 1-fluoro-2,2-diiodovinylarenes (Scheme 1).

As expected, **3a** was successfully obtained in 91% yield. *o*-, *m*-, and *p*-tolylpropiolic acids provided their corresponding products (**3b**, **3c**, and **3d**) in 88, 89, and 93% yield, respectively. Alkoxy-substituted arylpropiolic acids gave products **3e–h** in good yield. 1,1′-Biphenyl-4-ylpropiolic acid afforded **3i** in 85% yield. Arylpropiolic acids bearing ketone and ester groups coupled with **1a** to give their corresponding products (**3j** and **3k**) in 82 and 84% yield, respectively. 4-Fluoro- and 4-chlorophenylpropiolic acid exhibit good yields. Alkyl-substituted propiolic acids such as 2-octynoic acid, 2-hexynoic acid, and 2-pentynoic acid afforded the corresponding products **3n**, **3o**, and **3p** in 72%, 65%, and 59% yields, respectively. 1-Fluoro-2,2-diiodovinylarenes bearing ester, chloro, and fluoro groups also react with phenylpropiolic acid. As expected, all of the reactions gave the desired product in good yield.

Next, all of the substrates previously used in the monoalkynylation reaction were subjected to the optimal conditions for the dialkynylation reaction. In addition, a variety of aryl propiolic acids were reacted with several 1-fluoro-2,2-diiodovinylarenes under the dialkynylation reaction conditions. As shown in Scheme 2, most substrates afforded the desired dialkynylated product in good yield. It is noteworthy that monoalkynylated products were found in less than 4% yield in the reaction mixture in all cases. However, alkyl-substituted propiolic acids such as 2-octynoic acid did not give the desired product. Unfortunately, we failed to isolate **4i** and **4m** in pure form because they provided messy mixtures.

For comparison, the reaction using terminal alkynes was investigated. The two optimized conditions were employed in the reaction of **1a** and phenylacetylene. As shown in Scheme 3, when the reaction was conducted using DBU/DMSO, (*Z*)-**3a**

Scheme 1. Decarboxylative Monoalkynylation of 1[a]

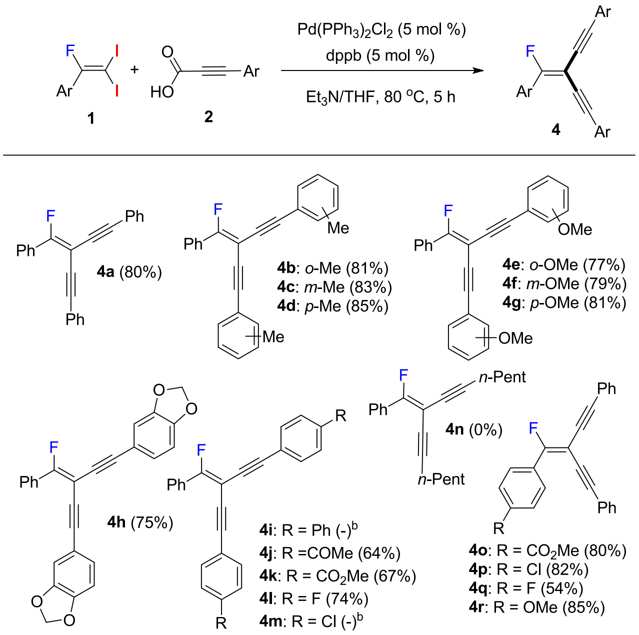


[a]Reaction conditions: **1** (1.0 mmol), **2** (2.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.025 mmol), dppb (0.025 mmol), and DBU (3.0 mmol) were reacted in DMSO at 100 °C for 5 h. Isolated yields are shown in parentheses.

and **4a** were formed in 85 and 8% yield, respectively. The reaction performed using Et_3N/THF provided (*Z*)-**3a** and **4a** in 5 and 70% yield, respectively. From these results, the reactions with terminal alkyne showed lower selectivity than those with alkynoic acids.

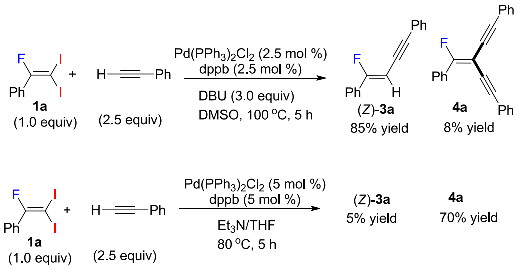
To study the hydrodeiodination process, several control experiments were carried out (Scheme 4). When **1a** and **2a** were reacted in the presence of D_2O under the optimized conditions, deuterium-exchanged (*Z*)-**3a** was formed. It was found that the reaction with **1a-D** also afforded the deuterium exchanged product. When **1a** was allowed to react with DBU in DMSO in the absence of the alkynoic acid, hydrodeiodinated product (*Z*)-**5** was formed in 91% yield. However, no (*E*)-**5** was observed in the reaction mixture. When the same reaction was conducted using Et_3N/THF, (*Z*)-**5** and (*E*)-**5** were formed in 35 and 10% yield, respectively. When these two reactions were carried out using anhydrous solvent, the yield of the hydrodeiodination products decreased. We also studied the ratio of **1a** and **2a** using Et_3N/THF. When 1.1 equiv of **2a** reacted with **1a**, **4a** and a mixture of (*E*)- and (*Z*)-**3a** were formed in 29 and 38% yield, respectively. When 2,2-diiodovinylbenzene which has no fluorine atom was allowed to react with *p*-tolylpropiolic acid under the standard conditions, unsymmetrical 1,3-diyne product was formed; however, the desired enynes were not found (see the Supporting Information).[16]

Scheme 2. Decarboxylative Dialkynylation of 1a[a]



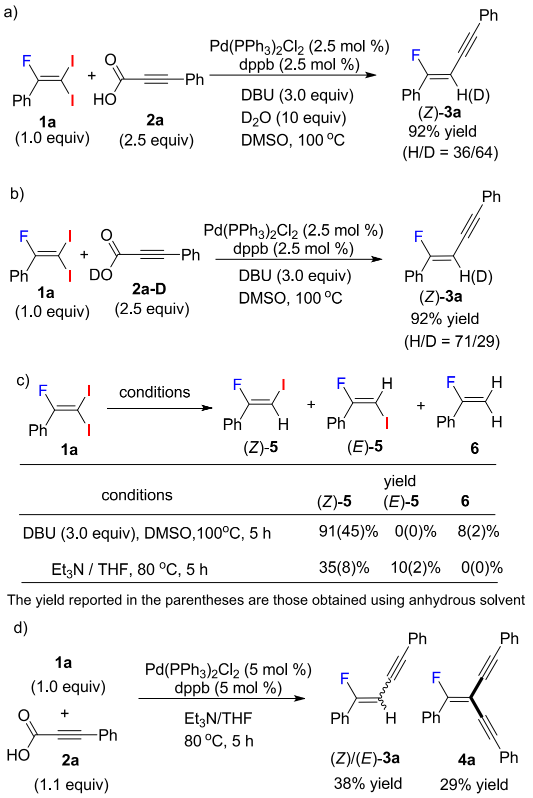
[a]Reaction conditions: **1** (1.0 mmol), **2** (2.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.05 mmol), and dppb (0.05 mmol) were reacted in Et_3N/THF (4.0 mL/4.0 mL) at 80 °C for 5 h. Isolated yields are shown in parentheses. [b]Not determined.

Scheme 3. Coupling Reactions Using Terminal Alkynes



On the basis of these control experiments, we proposed the mechanism for the coupling reactions, as shown in Scheme 5. In the reaction using DBU/DMSO, the hydrodeiodination reaction takes place followed by the Pd-catalyzed decarboxylative coupling reaction. However, the hydrodeiodination reaction may be slower when Et_3N/THF is used. Therefore, the Pd-catalyzed decarboxylative coupling reaction proceeds as the first step. Oxidative addition of Pd(0) to **1** gave intermediate **A**, and a subsequent decarboxylative exchange reaction with alkynoic acid affords palladium complex **B**. There are two possible pathways for the next step. Pathway **I** provides monoalkynlated compound **7** bearing a vinyl iodide group via reductive elimination. Pathway **II** is a continuous oxidative addition process that allows a further decarboxylative coupling reaction to occur. We propose that the pathway **II** is more predominant than pathway **I** because monocoupled product **7** was not observed in the reaction mixture. However, we cannot rule out pathway **III**, which involves the oxidative addition of **7** to Pd. It is noteworthy that the stereoselectivity of the oxidative addition to vinyl iodides is not clear at this point because a mixture of (*E*)- and (*Z*)-**3a** was formed, as shown in Scheme 4d.

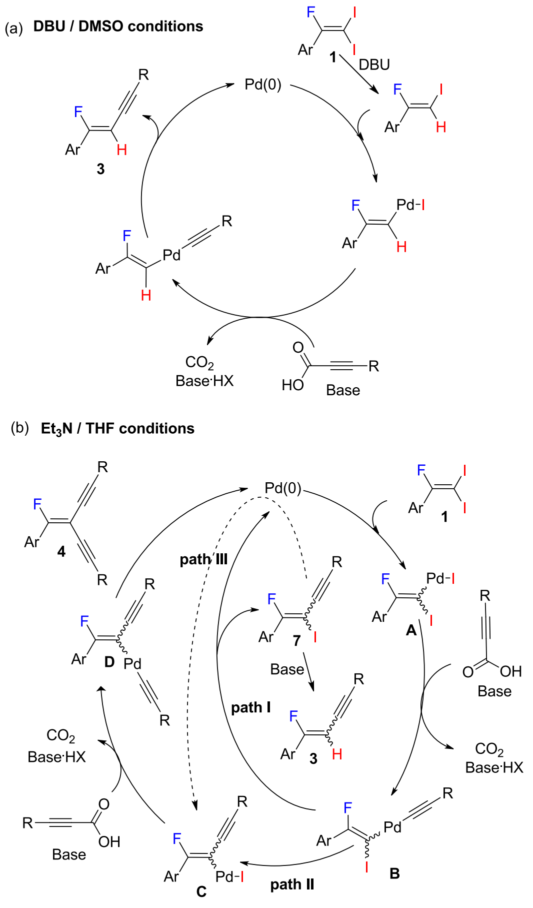
Scheme 4. Control Experiments



conditions	yield (Z)-5	yield (E)-5	yield 6
DBU (3.0 equiv), DMSO,100°C, 5 h	91(45)%	0(0)%	8(2)%
Et_3N / THF, 80 °C, 5 h	35(8)%	10(2)%	0(0)%

The yield reported in the parentheses are those obtained using anhydrous solvent

Scheme 5. Proposed Mechanism



In summary, we have developed the selective mono- and dialkynylation of 2-fluoro-1,1-diiodoarenes using a palladium-catalyzed decarboxylative coupling reaction. The catalytic system consisting of $Pd(PPh_3)_2Cl_2$ and dppb showed optimal results in both cases. Monoalkynyl hydrodeiodinated fluoroalkenes (*Z*)-**3** were formed using DBU/DMSO, whereas dialkynylfluoroalkenes **4** were formed using Et_3N/THF. These reaction methods provide the desired products in good yield with high selectivity and showed good functional group tolerance. In addition, we believe that these methods are very useful tools for the preparation of enynes and endiynes containing a fluorine atom.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02907.

Experimental procedures and spectral data for the products (PDF)

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Notes

The authors declare no competing financial interest.

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