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Palladium catalyzed mono and difunctionalization of hexafluorobut-2-yne

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ABSTRACT

The Pd (0) catalyzed one-pot mono and difunctionalization of hexafluorobut-2-yne is investigated. Styrenes and stilbenes can be obtained in high stereoselectivity by carbopalladation of phenylboronic acids and iodide benzenes. The reactions afford a facile access to a broad scope with good functional compatibility.

1. Introduction

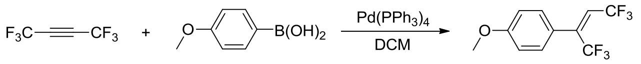
Trifluoromethylated alkenes have been widely used in light-emitting diodes (OLEDs) and anticancer drugs.[1,2] The incorporation of trifluoromethylated groups into olefins has attracted increasing attention because of the significant improvements in chemistry applications. Transition metal catalyzed carbometalation was an effective approach to installing the trifluoromethyl subunits, which could tolerate a wide variety of important organic functional groups,[3,4] and further multicomponent coupling across internal alkynes are easily transformed into tetrasubstitued alkenes.[5,6]

The controllable synthesis of α,β-trifluoromethylstilbenes under mild reaction conditions was particularly attractive,[7] and carbometalation of fluoroalkyne for introduction of trifluoromethylated groups into olefins would be advantageous. Burton[8] and co-workers found the reaction of arylcopper reagents addition to hexafluorobut-2-yne. Konno[9] reported that fluoroalkylated alkynes could undergo coupling reaction with aryl iodides and arylboronic acids. In our recent work, hexafluorobutyne was obtained from chlorohexafluorobutene through dehydrochlorination,[10] which enable the construction of α,β-trifluoromethylated styrenes and stilbenes respectively.[11] Herein, we present a palladium (0) catalyzed one-pot carbometalation reaction of hexafluorobutyne for the synthesis of hexafluoride styrene derivatives with good functional compatibility, and further coupling reaction involving aryl halides leading to the corresponding tetrasubstituted alkenes stereoselectively.

2. Results and discussion

Initially, the addition of (4-methoxyphenyl)boronic acid (**2a**) to 1,1,1,4,4,4-hexafluorobut-2-yne (**1**) was chosen as model reaction. In the absence of palladium catalyst, no desired product (**3a**) was observed (Table 1, entry 1). Then the influence of catalyst was examined, tetrakis(triphenylphosphine) palladium [$Pd(PPh_3)_4$] was found to be the best catalyst for the reaction, other palladium catalysts such as palladium dichloride ($PdCl_2$), palladium acetate

Table 1 Optimization of the carbometalation addition[a]



1 2a 3a

entry	[Pd]	solvent	yield[b] (%)
1	-	1,4-dioxane	0
2	$PdCl_2$	1,4-dioxane	15
3	$Pd(OAc)_2$	1,4-dioxane	40
4	$Pd(PPh_3)_2Cl_2$	1,4-dioxane	25
5	$Pd(PPh_3)_4$	1,4-dioxane	84
6	$Pd_2(dba)_3$	1,4-dioxane	51
7	$Pd(PPh_3)_4$	DMF	15
8	$Pd(PPh_3)_4$	THF	79
9	**$Pd(PPh_3)_4$**	**DCM**	**94 (91)**
10[c]	$Pd(PPh_3)_4$	DCM	89
11[c]	$Pd(PPh_3)_4$	1,4-dioxane	7

[a] Reaction conditions: **1** (3 mmol), **2a** (1 mmol), catalyst (5 mol%), solvent (2 mL), room temperature, 16 h.

[b] yields determined by ^1H and ^{19}F NMR, 4'-fluoroacetophenone as internal standard.

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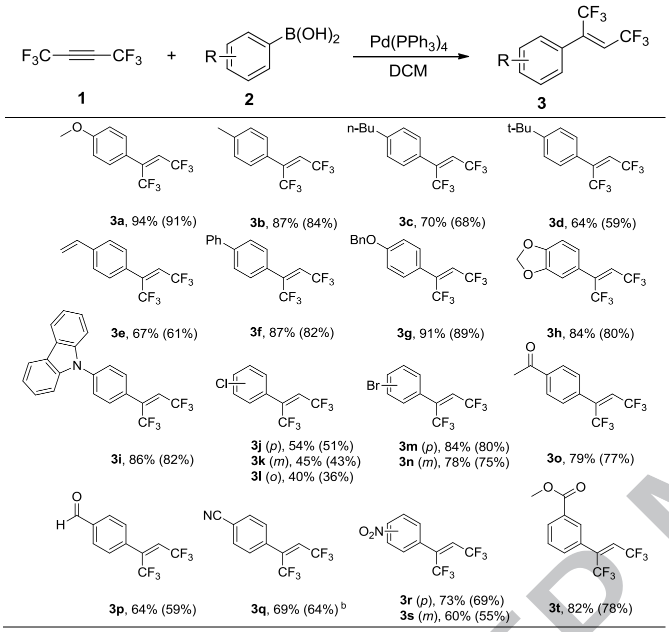
[c] catalyst (1 mol%).

[Pd(OAc)$_2$], Palladium bis(triphenylphosphine)dichloride [Pd(PPh$_3$)$_2$Cl$_2$], or tris(dibenzylideneacetone)dipalladium [Pd$_2$(dba)$_3$] was inferior (Table 1, entries 2-6). Since the solvent has a significant influence on the solubility of fluoroalkyne, several solvents including *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF) and dichloromethane (DCM) were screened with the latter providing the best yield (Table 1, entries 7-9). DCM was found to be quite successful even the catalyst loadings reducing to 1 mol% (Table 1, entry 10), surprisingly, the yield of desired alkene in 1,4-dioxane was dramatically decreased from 84% to only 7% (Table 1, entry 11).

Table 2 Carbopalladation of various boronic acids[a]



3a, 94% (91%)
3b, 87% (84%)
3c, 70% (68%)
3d, 64% (59%)
3e, 67% (61%)
3f, 87% (82%)
3g, 91% (89%)
3h, 84% (80%)
3i, 86% (82%)
3j (*p*), 54% (51%)
3k (*m*), 45% (43%)
3l (*o*), 40% (36%)
3m (*p*), 84% (80%)
3n (*m*), 78% (75%)
3o, 79% (77%)
3p, 64% (59%)
3q, 69% (64%)[b]
3r (*p*), 73% (69%)
3s (*m*), 60% (55%)
3t, 82% (78%)

[a] Reaction conditions: **1** (3 mmol), **2** (1 mmol), Pd(PPh$_3$)$_4$ (5 mol%), DCM (2 mL), room temperature, 16 h, yields determined by ^{1}H and ^{19}F NMR, 4'-fluoroacetophenone as internal standard.

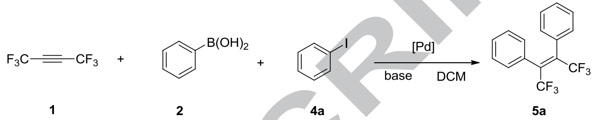
[b] KHCO$_3$ (3 mmol).

This strategy was applicable to a variety of phenylboronic acids, giving the trisubstituted products with various functional groups as a single stereoisomer. The results are summarized in Table 2. Generally, substrates bearing electron donating or electron withdrawing groups were suitable for this reaction, leading to the desired α,β-trifluoromethylstyrenes in moderate to good yields in *cis* fashion. Substrates with electron-rich group like methoxy (Table 2, **3a**), methyl (Table 2, **3b**), butyl (Table 2, **3c** and **3d**), vinyl (Table 2, **3e**), phenyl (Table 2, **3f**) or benzyl (Table 2, **3g**) on the *para*-position of the aryl ring could participate in this transformation smoothly. The heteroaryl boronic acids (Table 2, **3h** and **3i**) were also well tolerated under the optimized conditions. *Para*-, *meta*- or *ortho*-halides substituents (Table 2, **3j-3n**) did not hamper the reactivity, which might be useful for further manipulation. Aryl boronic acids bearing electron poor moieties such as carbonyl (Table 2, **3o** and **3p**), nitro (Table 2, **3r** and **3s**) or ester (Table 2, **3t**) functionalities were compatible with the reaction. To our delight, cyano substituent remained intact, albeit employing a weaker base was better for the formation of **3q**.

In order to further demonstrate the utility of this protocol, a palladium catalyzed three-component coupling reaction was examined. The procedure was an effective tool for producing stilbenes,[12] investigation commenced with less hindered boronic acid and iodide benzene (**4a**). Palladium sources were revaluated (Table 3, entries 1-5), [Pd(PPh$_3$)$_4$] remained the best catalyst. After various bases were introduced in the transformation (Table 3, entries 6-12), K$_2$CO$_3$ was found to be the most efficient, increasing the yield of **5a** to 51%.

The three-component coupling process was further explored, and compound **5** was obtained as the major product with high *Z*-selectivities. An elevated temperature was used which simultaneously increased the side reaction, as a result, tetrasubstituent was contaminated by biaryl and other byproducts. For electron-rich reactants (Table 4, **5b**), adducts obtained in moderated yield, nitro group provided target compound in an obviously dropping yield (Table 4, **5c**).

Table 3 Three component coupling reaction[a]

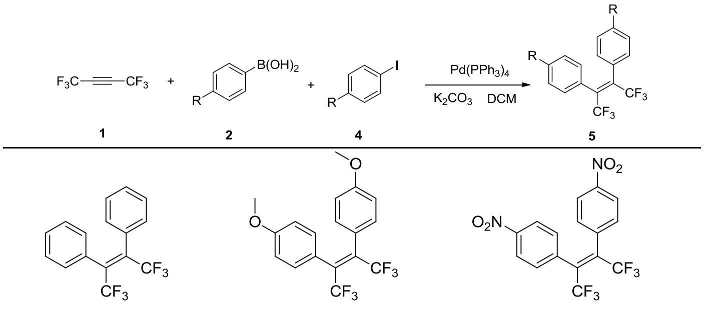


entry	[Pd]	base	yield[b] (%)
1	Pd(PPh$_3$)$_2$Cl$_2$	K$_2$CO$_3$	28
2	Pd(OAc)$_2$	K$_2$CO$_3$	trace
3	Pd(PhCN)$_2$Cl$_2$	K$_2$CO$_3$	18
4	Pd$_2$(dba)$_3$	K$_2$CO$_3$	22
5	**Pd(PPh$_3$)$_4$**	**K$_2$CO$_3$**	**51 (44)**
6	Pd(PPh$_3$)$_4$	Na$_2$CO$_3$	27
7	Pd(PPh$_3$)$_4$	Cs$_2$CO$_3$	35
8	Pd(PPh$_3$)$_4$	KHCO$_3$	38
9	Pd(PPh$_3$)$_4$	KH$_2$PO$_4$	12
10	Pd(PPh$_3$)$_4$	K$_2$HPO$_4$•3H$_2$O	45
11	Pd(PPh$_3$)$_4$	K$_3$PO$_4$•7H$_2$O	34
12	Pd(PPh$_3$)$_4$	NaOAc	20

[a] Reaction conditions: **1** (3 mmol), **2** (1 mmol), **3a** (1 mmol), catalyst (5 mol%), DCM (2 mL), 100 °C, 16 h.

[b] yields determined by ^{1}H and ^{19}F NMR, 4'-fluoroacetophenone as internal standard.

Table 4 Coupling reaction of hexafluorobutyne[a]



5a, 51% (44%)
5b, 47% (41%)
5c, 41% (36%)

[a] Reaction conditions: **1** (3 mmol), **2** (1 mmol), **4** (1 mmol), Pd(PPh$_3$)$_4$ (5 mol%), K$_2$CO$_3$ (3 mmol), DCM (2 mL), 100 °C, 16 h, yields determined by ^{1}H and ^{19}F NMR, 4'-fluoroacetophenone as internal standard.

3. Conclusions

In summary, an efficient addition of boronic acids with functional groups to hexafluorobut-2-yne over a palladium catalyst was developed, featuring a *syn* addition process. The reactions could be carried out under mild conditions, allowing for the synthesis of a variety of trifluoromethylated containing alkenes. Further optimization for difunctional applicability is underway in our laboratory.

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Supplementary data

Text files giving additional experimental and characterization data. Copies of the ^{1}H, ^{13}C and ^{19}F NMR spectra of the products produced in this study. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/xxx.

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Highlights

- One-pot mono and difunctionalization of hexafluorobut-2-yne is investigated respectively.
- Trisubstituted and tetrasubstituted α,β-trifluoromethylstilbenzenes can be obtained both in high *Z*-stereoselectivity.
- The reaction featuring simple manipulation.
- The reaction could be carried out under mild conditions.
- The reaction affords a facile access for a broad scope with good functional compatibility.