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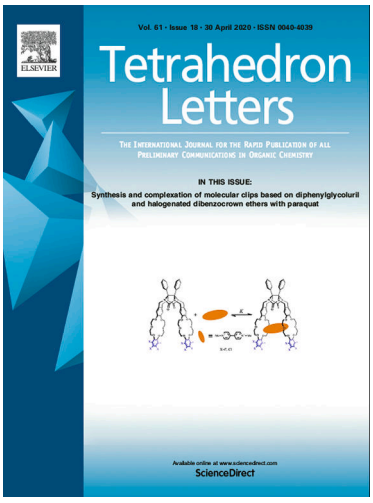

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PII: S0040-4039(20)30391-9
DOI: https://doi.org/10.1016/j.tetlet.2020.151948
Reference: TETL 151948

To appear in: *Tetrahedron Letters*

Received Date: 8 February 2020
Revised Date: 9 April 2020
Accepted Date: 13 April 2020

Please cite this article as: Ding, L., Han, S., Chen, X., Li, L., Li, J., Zou, D., Wu, Y., Wu, Y., An efficient protocol for the synthesis of monofluoroalkylated (hetero)arenes via Pd-catalyzed α-(hetero)arylation of α-fluoroketones with (hetero)aryl bromides, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.151948

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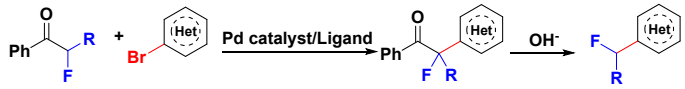

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An efficient protocol for the synthesis of monofluoroalkylated (hetero)arenes via Pd-catalyzed α-(hetero)arylation of α-fluoroketones with (hetero)aryl bromides

Licheng Ding[a], Shuaijun Han[a], Xiaoyu Chen[a], Linlin Li[a], Jingya Li[b], Dapeng Zou[a,*], Yangjie Wu[a,*], Yusheng Wu[a,b,c,*]

[a]College of Chemistry, Henan Key Laboratory of Chemical Biology and Organic Chemistry, Zhengzhou University, Zhengzhou 450052, PR China
[b]Tetranov Biopharm, LLC. And Collaborative Innovation Center of New Drug Research and Safety Evaluation, Zhengzhou, 450052, PR China
[c]Tetranov International, Inc., 100 Jersey Avenue, Suite A340, New Brunswick, NJ 08901, USA

* Corresponding author. Tel.: (+86)-371-6776-6865; fax: +86-371-6776-1390; e-mail: zdp@zzu.edu.cn or wyj@zzu.edu.cn
* Corresponding author. Tel.: (+ 1)-732-253-7326; fax: (+ 1)-732-253-7327; e-mail: yusheng.wu@tetranovglobal.com

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Palladium-catalyzed
Base-induced
α-(hetero)arylation
Monofluoroalkylation.

ARTICLE INFO

ABSTRACT

An efficient synthesis of monofluoroalkylated N-heteroarenes using α-fluoroketones as monofluoroalkyl reagents is developed. A variety of novel α-(hetero)aryl-α-fluoroketones and monofluoroalkylated N-heteroarenes were obtained in moderate to good yields. Notable advantages of this protocol include a low catalyst loading, easily prepared monofluoroalkyl reagents and wide substrate scope.

Introduction

Fluorine-containing organic compounds play an extremely important role in biomedical, agricultural and material sciences, because the introduction of fluorine or fluorinalkyl moieties into organic compounds can significantly influence their lipophilic, metabolic stability and bioavailability properties (Figure 1).[1] As important fluorinated moieties, monofluoroalkylated (hetero)arenes have been widely used in pharmaceutical products.[2] In particular, several of biologically active compounds, including the afloqualone, (6R)-indaziflam and the ^{18}F-ibuprofen ester, contain a monofluoroalkyl group (CHF-alkyl) as a significant motif.[3] Despite its importance, the incorporation of monofluoroalkyl group (CHF-alkyl) into (hetero)arenes has been studied to a lesser extent and is still challenging.[4]

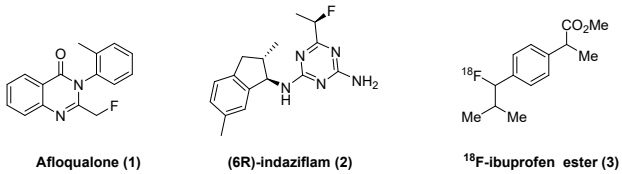
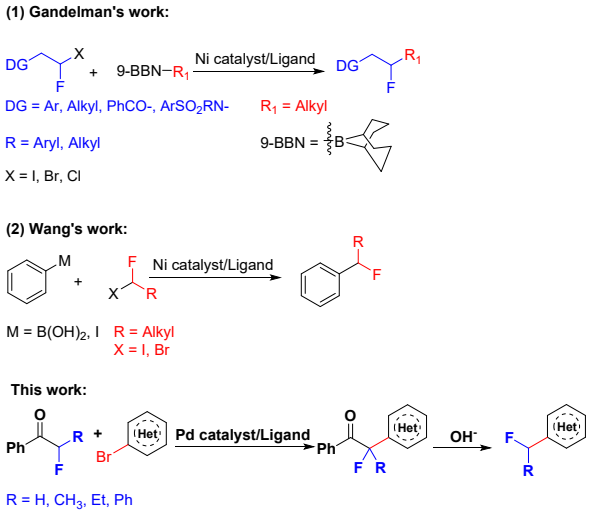


Figure. 1. Bioactive molecules containing monofluoroalkylated heteroarene.

Along with the development of direct C-H functionalization reactions, a series of methods for direct C-H fluorination at the benzylic position were developed.[5] However, the relatively poor functional-group compatibility might diminish the general application of these methods. Meanwhile, the nickel-catalyzed monofluoroalkylation of arenes using 1-bromo-1-fluoroalkanes as monofluoroalkylating reagents was reported by Gandelman in 2014 (Scheme 1).[6] Subsequently, Wang described a combinatorial nickel-catalyzed system for the efficient construction of monofluoroalkylated arenes using readily avaliable arylboronic acids and unactived 1-fluoro-1-iodoalkanes.[7] Recently, a nickel-catalyzed monofluoroalkylation through reductive coupling of aryl halides and monofluoroalkyl halides was developed by Wang.[8] Despite great progress in the monofluoroalkylation of arenes, continuous efforts are still needed, especially for monofluoroalkylation of the (hetero)arenes.



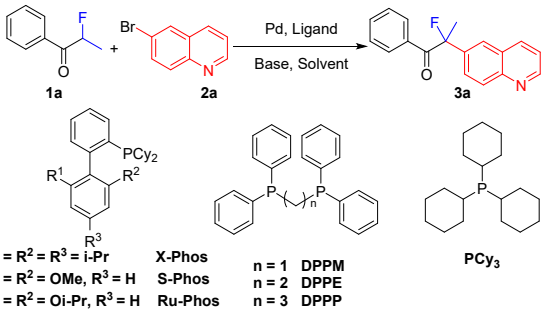
Scheme 1. The synthesis of monofluoroalkylated (hetero)arenes.

The benzoyl was found to be a multifunctional group, which enabled the cross-coupling of aryl halides with α-aryl-ketones[9], as well as the further transformations of these products[10]. Therefore, Pd-catalyzed arylation of α-fluoroketones have become an efficient method for the construction of carbon-carbon bonds. In 2012, Qing developed a versatile method to prepare α-aryl-α-fluoroketones by palladium-catalyzed direct α-arylation of α-fluoroketones with structurally diverse aryl bromides.[9f] However, the synthesis of monofluoroalkylated N-heteroarenes was not investigated. As a part of our ongoing efforts on fluorine chemistry[11], herein, we report an efficient protocol for the synthesis of a series of monofluoroalkylated N-heteroarenes via Pd-catalyzed α-(hetero)arylation of α-fluoroketones with bromo-substituted N-heteroarenes.

Results and Discussion

At first, 2-fluoro-1-phenylpropan-1-one (**1a**) and 6-bromoquinoline (**2a**) were chosen as the model substrates to optimize the reaction conditions, and the results were summarized in Table 1. When the reaction of **1a** and **2a** was performed in the presence of $Pd(OAc)_2$ (5.0 mol%), X-phos (10.0 mol%), and Cs_2CO_3 (2.0 equiv, 0.6 mmol) in toluene at 120 °C for 24 h, **3a** was obtained in 25% yield (Table 1, entry 1). Then, various monophosphine and bisphosphine ligands were tested,[9, 12] and PCy_3 was proved to be an optimal choice (Table 1, entries 2-7). When $Pd(OAc)_2$ was switched to $PdCl_2$, the yield of **3a** was improved to 93% (entry 8). Other palladium catalysts were found to be less effective for the transformation (Table 1, entries 9-13). When other commonly used bases such as CsF, ^{t}BuONa, KOH, and K_3PO_4 were investigated, none of them was found to be effective for the reaction (Table 1, entries 14-17). When catalyst loading was studied, a good yield was obtained in the combination with $PdCl_2$ (2.0 mol%), and PCy_3 (4.0 mol%) (Table 1, entries 18-21). Furthermore, when the reaction was carried out with **1a** (2.0 equiv, 0.6 mmol), **2a** (1.0 equiv, 0.3 mmol), the yield of **3a** was slightly increased (Table 1, entries 22-23). Screening for various solvents indicated that 1,4-dioxane was a better choice in the reaction process (Table 1, entries 24-25). Decreasing reaction temperature or shorting reaction time resulted in lower yield (Table 1, entries 26-27). Finally, the optimized reaction conditions were determined as **1a** (2.0 equiv, 0.6mmol), **2a** (1.0 equiv, 0.3 mmol), $PdCl_2$ (2.0 mol%), PCy_3 (4.0 mol%), Cs_2CO_3 (2.0 equiv, 0.6 mmol), 1,4-dioxane (2.0 mL), at 120 °C under Ar for 24 h.

Table 1. Optimization of reaction conditions for the synthesis of monofluoroalkylated α-fluoroketones: optimization of conditions.[a]



Entry	Catalyst	Ligand	Base	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	X-Phos	Cs_2CO_3	toluene	25
2	$Pd(OAc)_2$	S-Phos	Cs_2CO_3	toluene	44
3	$Pd(OAc)_2$	Ru-Phos	Cs_2CO_3	toluene	27
4	$Pd(OAc)_2$	DPPM	Cs_2CO_3	toluene	12
5	$Pd(OAc)_2$	DPPE	Cs_2CO_3	toluene	84
6	$Pd(OAc)_2$	DPPP	Cs_2CO_3	toluene	42
7	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	toluene	89
8	$PdCl_2$	PCy_3	Cs_2CO_3	toluene	93(86)
9	$Pd(PPh_3)_4$	PCy_3	Cs_2CO_3	toluene	83
10	$Pd(CF_3COO)_2$	PCy_3	Cs_2CO_3	toluene	79
11	$Pd(dba)_2$	PCy_3	Cs_2CO_3	toluene	71
12	$PdCl_2$(dppf)	PCy_3	Cs_2CO_3	toluene	76
13	$PdCl_2$(COD)	PCy_3	Cs_2CO_3	toluene	85
14	$PdCl_2$	PCy_3	CsF	toluene	trace
15	$PdCl_2$	PCy_3	^{t}BuONa	toluene	n. r.
16	$PdCl_2$	PCy_3	KOH	toluene	n. r.
17	$PdCl_2$	PCy_3	K_3PO_4	toluene	trace
18[d]	$PdCl_2$	PCy_3	Cs_2CO_3	toluene	88
19[e]	$PdCl_2$	PCy_3	Cs_2CO_3	toluene	88
20[f]	$PdCl_2$	PCy_3	Cs_2CO_3	toluene	24
21[g]	$PdCl_2$	PCy_3	Cs_2CO_3	toluene	88
22[g,h]	$PdCl_2$	PCy_3	Cs_2CO_3	toluene	89
23[g,i]	$PdCl_2$	PCy_3	Cs_2CO_3	toluene	79
24[g,h]	$PdCl_2$	PCy_3	Cs_2CO_3	1,4-dioxane	92(86)
25[g,h]	$PdCl_2$	PCy_3	Cs_2CO_3	xylene	82
26[g,h,j]	$PdCl_2$	PCy_3	Cs_2CO_3	1,4-dioxane	79
27[g,h,k]	$PdCl_2$	PCy_3	Cs_2CO_3	1,4-dioxane	63

[a] Reaction conditions: **1a** (1.0 equiv, 0.3 mmol), **2a** (2.0 equiv, 0.6 mmol), [Pd] (5.0 mol%), Ligand (10.0 mol%), Cs_2CO_3 (2.0 equiv, 0.6 mmol), solvent (2.0 mL), at 120 °C under argon for 24 h.

[b] HPLC yield, isolated yields are shown in parentheses.

[c] n.r.= no reaction.

[d] $PdCl_2$ (3.0 mol%), PCy_3 (10.0 mol%).

[e] $PdCl_2$ (2.0 mol%), PCy_3 (10.0 mol%).

[f] $PdCl_2$ (1.0 mol%), PCy_3 (10.0 mol%).

[g] $PdCl_2$ (2.0 mol%), PCy_3 (4.0 mol%).

[h] **1a** (2.0 equiv, 0.6 mmol), **2a** (1.0 equiv, 0.3 mmol).

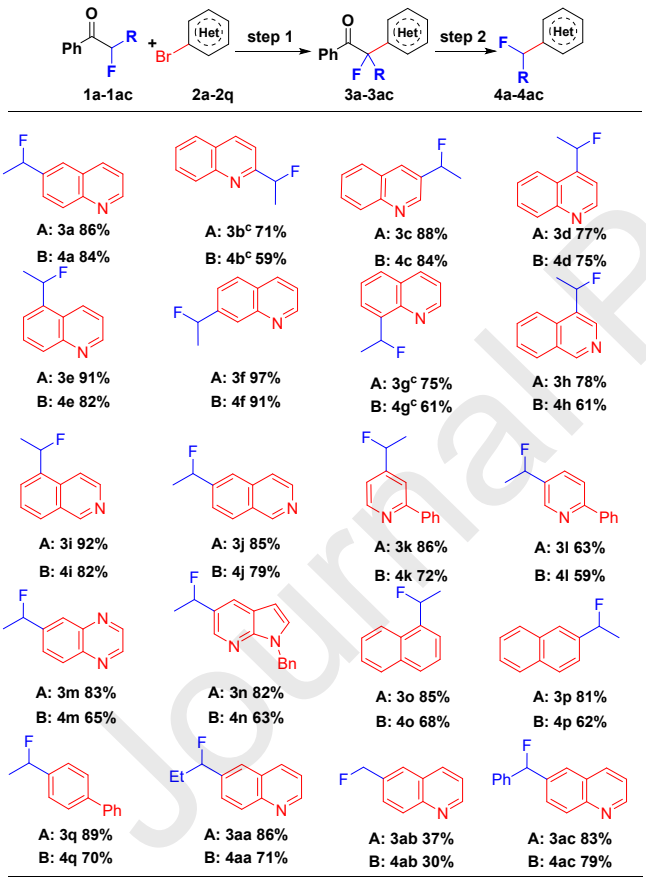
[i] **1a** (1.5 equiv, 0.45 mmol), **2a** (1.0 equiv, 0.3 mmol).

[j] 100 °C.

Under the optimized conditions, the reaction of 2-fluoro-1-phenylpropan-1-one (**1a**) with (hetero)aryl bromides (**2a-2q**) were investigated (Table 2). The α-(hetero)arylation reaction of 2-fluoro-1-phenylpropan-1-one (**1a**) with different bromoquinolines proceeded smoothly to give the desired products (**3a-3g**) in good to excellent yields, while 2- and 8-bromoquinoline required slightly higher loading of catalyst. Bromoisoquinolines could also be used as effective substrates for this transformation (**3h-3j**). Moreover, various bromo-substituted N-heteroarenes, such as pyridine, quinoxaline and 1H-pyrrolo[2,3-b]pyridine underwent the reaction smoothly to give the target products (**3k-3n**) in 63-86% yields. Bromonaphthalenes and bromobiphenyl reacted with 2-fluoro-1-phenylpropan-1-one (**1a**) to give (**3o-3q**) in excellent yields.

To establish the scope of this protocol, different ketone derivatives were then tested under the optimized conditions. Fortunately, 2-fluoro-1-phenylbutan-1-one (**1aa**) and 2-fluoro-1,2-diphenylethanone (**1ac**) gave the desired products in good yields (**3aa**, **3ac**). Whereas, α-(hetero)arylation reaction of 2-fluoro-1-phenylethanone (**1ab**) gave the target product in lower yield (**3ab**).

Table 2. Substrate scope [a,b,c]



[a] Reaction conditions: step 1, **1** (2.0 equiv, 0.6 mmol), **2** (1.0 equiv, 0.3 mmol), $PdCl_2$ (2.0 mol%), PCy_3 (4.0 mol%), Cs_2CO_3 (2.0 equiv, 0.6 mmol), 1,4-dioxane (2.0 mL), at 120 °C under Ar for 24 h; step 2, KOH (300.0 mg), H_2O (50.0 mg), 1,4-dioxane (2.0 mL), at 120 °C for 3 h.

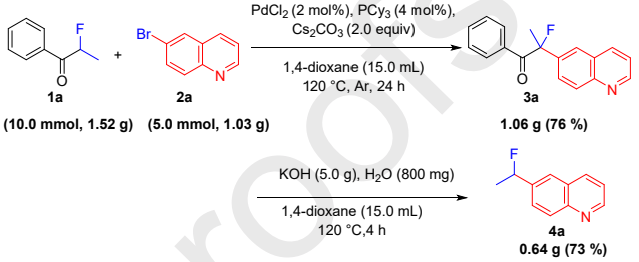
[b] Isolated yields. A: The yield of **2** to **3**. B: The yield of **2** to **4**.

[c] step 1, $PdCl_2$ (5.0 mol%), PCy_3 (10.0 mol%).

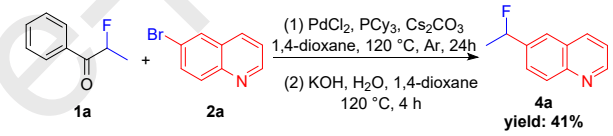
Subsequently, the deprotection process of benzoyl group was also studied. The result indicated that the simple condition worked well for most of the acquired α-(hetero)aryl products (**3a-4q**, **4aa-4ac**), as shown in Table 2.

To further demonstrate the utility of this reaction, we subsequently carried out a gram-scale reaction of 2-fluoro-1-phenylpropan-1-one (**1a**, 1.52 g, 10 mmol) and 6-bromoquinoline (**2a,** 1.03 g, 5.0 mmol) under the optimal reaction conditions (Scheme 2). As a result, the target products (**3a**) and (**4a**) were obtained in 76% and 73% yield, respectively. A one-pot two-steps synthesis of 6-(1-fluoroethyl)quinoline (**4a**) was then investigated (Scheme 3). Unfortunately, compared with the above two-steps method, the one-pot protocol gave the desired **4a** in only 41% yield (Scheme 3).

Scheme 2. Gram-scale reaction.

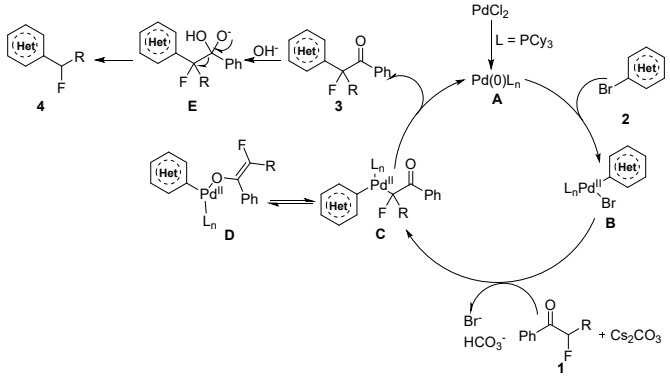


Scheme 3. A one-pot two-steps synthesis of 6-(1-fluoroethyl)quinolone.



In the basis of previous reports[12, 13] and our research, a plausible mechanism is proposed (Scheme 4). Firstly, oxidative addition of the Pd(0) catalytic species **A** with bromo-substituted N-heteroarenes **2** formed Pd(II) complex **B**. Subsequently, α-fluoroketone **1** converted to the enolate compound in the presence of Cs_2CO_3[12g, 12h]. The nucleophilic enolate compound **1** could attack the Br in coordinated bromide complex **B** to produce two possible coordination modes of the palladium enolate complexes (**C** or **D**)[12b, 12e, 12f], which underwent reductive elimination to generate α-(hetero)aryl-α-fluoroketone **3**. Finally, OH^- attacked the carbonyl group of compound **3** to form intermediate **E**. Because the introduction of the (hetero)aromatic ring could stabilize the negative charge to a greater extent[13c], the intermediate **E** processed C-C bond cleavage to form the final monofluoroalkylated N-heteroarenes **4**.

Scheme 4. Plausible Mechanism.



In conclusion, we have developed an efficient strategy for the synthesis of monofluoroalkylated N-heteroarenes via Pd-catalyzed α-(hetero)arylation of α-fluoroketones with bromo-substituted N-heteroarenes. A series of novel α-(hetero)aryl-α-fluoroketones and monofluoroalkylated N-heteroarenes were obtained in moderate to excellent yields. Moreover, this process has demonstrated high catalytic reactivity and broad substrate scope. It would be attractive and useful in laboratory methods, industrial processes, and pharmaceutical researchs.

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Declaration of interests

☑ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Highlights

• A new approach to synthesize α-(hetero)aryl-α-fluoroketones and monofluoroalkylated N-heteroarenes
• The catalytic system features a low catalyst loading
• Easily prepared monofluoroalkyl reagents

An efficient protocol for the synthesis of monofluoroalkylated (hetero)arenes via Pd-catalyzed α-(hetero)arylation of α-fluoroketones with (hetero)aryl bromides

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Licheng Ding, Shuaijun Han, Xiaoyu Chen, Linlin Li, Jingya Li, Dapeng Zou*, Yusheng Wu*, Yangjie Wu*