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Generation of 4-polyfluoroaryl pyrrolo[1,2-*a*]quinolines *via* C–H bond activation†

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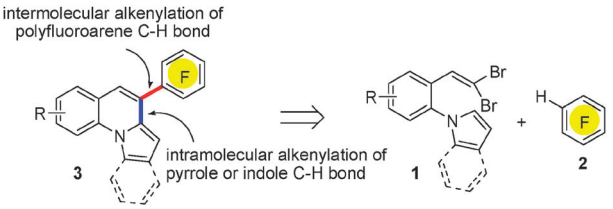
A novel and efficient preparation of 4-polyfluoroaryl pyrrolo-[1,2-*a*]quinolines *via* a palladium-catalyzed reaction of 1-[2-(2,2-dibromoethenyl)phenyl]-1*H*-pyrrole with polyfluoroarene is described. This transformation is efficient, leading to the corresponding products in good yields.

It is well known that polyfluorinated compounds have an important role in medicinal chemistry[1] and material science.[2] Continuous efforts have been devoted to the generation of molecules containing the polyfluoroarene structure. Recently, we have focused on fluorinated natural product-like compounds due to their remarkable effects on biological activities. As a part of our research in the construction of natural product-like compounds,[3] we are interested in the preparation of polyfluoroaryl substituted pyrrolo[1,2-*a*]quinolines. Pyrrolo[1,2-*a*]-quinoline and its derivatives are found in a wide variety of biologically important molecules,[4] and their applications with electron transport properties have been reported.[5] We anticipated that the polyfluoroaryl substituted pyrrolo[1,2-*a*]quinolines would be beneficial for various biological evaluations. Therefore, we initiated a program for rapid access to polyfluoroaryl pyrrolo-[1,2-*a*]quinolines.

Recent work on the synthesis of polyfluorinated aromatic compounds *via* direct coupling reactions of C–H bonds[6] of polyfluoroarenes with aryl and alkenyl halides has been attractive in organic synthesis.[7,8] In the meantime, Lautens and others reported[9–12] the formation of heterocycles using *gem*-dihalovinyl systems. The reactivity of *gem*-dihalovinyl systems and the efficiency of C–H activation of polyfluorinated aromatic compounds prompted us to consider the synthetic feasibility of the reaction of 1-(2-(2,2-dibromovinyl)phenyl)-1*H*-pyrrole **1** with polyfluoroarene **2** (Scheme 1). We envisaged that an intermolecular alkenylation of a polyfluoroarene C–H bond and an intramolecular alkenylation of a pyrrole or indole C–H bond in one step would be a good vehicle for the efficient assembly of pyrrolo[1,2-*a*]quinolines **3**. Herein, we describe the results of an investigation that has led to the discovery of a novel route to 4-polyfluoroaryl pyrrolo[1,2-*a*]quinolines *via* a palladium-catalyzed C–H bond activation of 1-[2-(2,2-dibromoethenyl)-phenyl]-1*H*-pyrrole with polyfluoroarene.



Scheme 1 Proposed synthetic route for the generation of polyfluoroaryl-substituted pyrrolo[1,2-*a*]quinolines.

Conditions for the palladium-catalyzed C–H bond activation were explored using 1-[2-(2,2-dibromoethenyl)phenyl]-1*H*-pyrrole **1a** and perfluoroarene **2a** as substrates. Initially, the reaction was carried out with $Pd(OAc)_2$ (5 mol%), S-Phos (10 mol%), and Cs_2CO_3 (3.0 equiv.) in 1,4-dioxane at 100 °C under a nitrogen atmosphere (Table 1, entry 1). Gratifyingly, the expected 4-(perfluoroaryl)pyrrolo[1,2-*a*]quinoline **3a** was formed and isolated in 45% yield. With this promising result in hand, we then focused on the selection of solvent. The yield was increased to 58% when toluene was used (Table 1, entry 2). We further screened different ligands. No desired product was detected without the addition of a phosphine ligand in a control experiment (data not shown in Table 1). The reaction gave rise to the best result when Ru-Phos was employed as the ligand (Table 1, entry 8). Switching the ligand to others proved to be unfruitful. Only a trace amount of product was observed when the ligand was replaced by Xant-Phos or DPPF (Table 1, entries 5 and 9). We were pleased to discover that the yield was increased to 90% when the temperature was lowered to 90 °C (Table 1, entry 11), while the yield was inferior when the reaction was performed at 110 °C or 80 °C. Screening other bases and palladium sources revealed that the combination of Cs_2CO_3 and $Pd(OAc)_2$ gave the best yield (Table 1, entries 13–17).

The generality of this process was explored under the optimal reaction conditions involving 5 mol% of $Pd(OAc)_2$, 10 mol% of Ru-Phos, 3.0 equiv. of Cs_2CO_3 in toluene at 90 °C (Table 2).[13] Various 1-[2-(2,2-dibromoethenyl)phenyl]-1*H*-pyrrole **1** and polyfluoroarenes **2** were evaluated. A wide range

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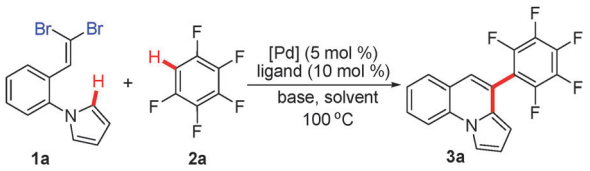
Table 1 Initial studies for the palladium-catalyzed reaction of 1-[2-(2,2-dibromoethenyl)phenyl]-1*H*-pyrrole **1a** with perfluoroarene **2a**[a]



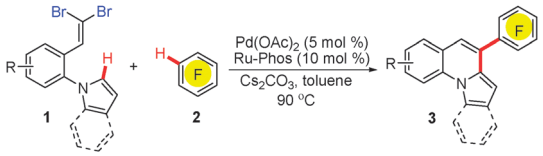
Entry	[Pd]	Ligand	Base	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	S-Phos[f]	Cs_2CO_3	Dioxane	45
2	$Pd(OAc)_2$	S-Phos	Cs_2CO_3	Toluene	58
3	$Pd(OAc)_2$	S-Phos	Cs_2CO_3	MeCN	49
4	$Pd(OAc)_2$	S-Phos	Cs_2CO_3	DMF	14
5	$Pd(OAc)_2$	Xant-Phos[g]	Cs_2CO_3	Toluene	Trace
6	$Pd(OAc)_2$	DavePhos[h]	Cs_2CO_3	Toluene	21
7	$Pd(OAc)_2$	X-Phos[i]	Cs_2CO_3	Toluene	58
8	$Pd(OAc)_2$	Ru-Phos[j]	Cs_2CO_3	Toluene	77
9	$Pd(OAc)_2$	DPPF[k]	Cs_2CO_3	Toluene	Trace
10[c]	$Pd(OAc)_2$	Ru-Phos	Cs_2CO_3	Toluene	75
11[d]	$Pd(OAc)_2$	Ru-Phos	Cs_2CO_3	Toluene	90
12[e]	$Pd(OAc)_2$	Ru-Phos	Cs_2CO_3	Toluene	67
13[d]	$Pd(OAc)_2$	Ru-Phos	K_2CO_3	Toluene	Trace
14[d]	$Pd(OAc)_2$	Ru-Phos	Ag_2CO_3	Toluene	Trace
15[d]	$Pd(OAc)_2$	Ru-Phos	K_3PO_4	Toluene	48
16[d]	$PdCl_2$	Ru-Phos	Cs_2CO_3	Toluene	31
17[d]	$Pd_2(dba)_3$	Ru-Phos	Cs_2CO_3	Toluene	52

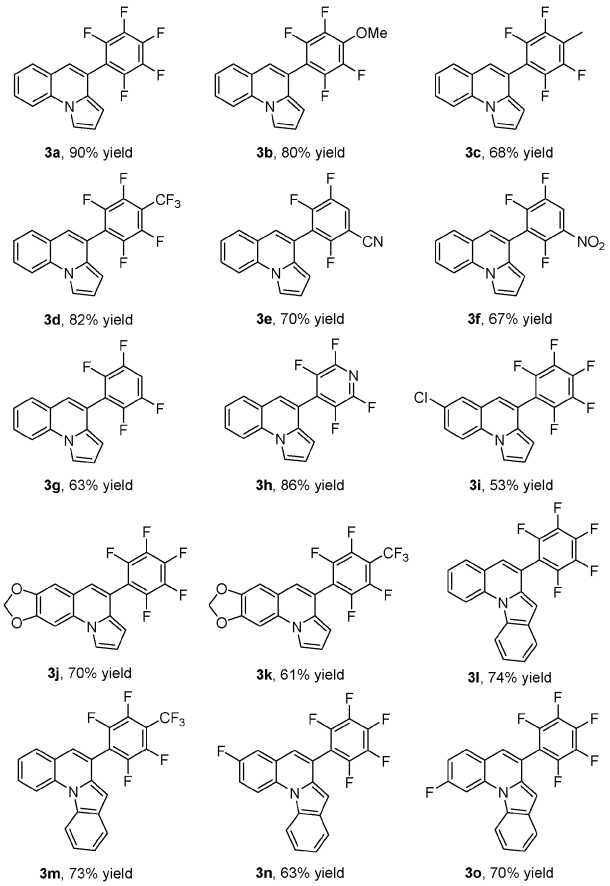
[a] Reaction conditions (unless otherwise specified): **1a** (0.4 mmol), **2a** (3 equiv.), [Pd] (5 mol%), ligand (10 mol%), and base (3 equiv.) in solvent (2.0 mL), at 100 °C. [b] Isolated yield based on 1-[2-(2,2-dibromoethenyl)phenyl]-1*H*-pyrrole **1a**. [c] The reaction was performed at 110 °C. [d] The reaction occurred at 90 °C. [e] The reaction occurred at 80 °C. [f] Dicyclohexyl(2′,6′-dimethoxy-[1,1′-biphenyl]-2-yl)phosphine. [g] (9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine). [h] 2′-(Dicyclohexylphosphino)-*N*,*N*-dimethyl-[1,1′-biphenyl]-2-amine. [i] Dicyclohexyl(2′,4′,6′-triisopropyl-[1,1′-biphenyl]-2-yl)phosphine. [j] Dicyclohexyl(2′,6′-diisopropoxy-[1,1′-biphenyl]-2-yl)phosphine. [k] 1,1′-Bis(diphenylphosphino)-ferrocene.

of polyfluoroarenes were employed and tolerated in the reaction. For example, 1-[2-(2,2-dibromoethenyl)phenyl]-1*H*-pyrrole **1a** underwent the reaction with 1,2,4,5-tetrafluoro-3-methoxybenzene leading to the expected product **3b** in 80% yield. Compound **3c** was obtained in 68% yield when 1,2,4,5-tetrafluoro-3-methylbenzene was used as a reactant. 1,2,4,5-Tetrafluoro-3-(trifluoromethyl)benzene was a good partner as well, which afforded the desired product **3d** in 82% yield. Further investigation revealed that reaction of 1-[2-(2,2-dibromoethenyl)-phenyl]-1*H*-pyrrole **1a** with cyano or nitro-substituted polyfluoroarene also worked well to furnish the corresponding product in good yields. Interestingly, incorporation of 2,3,5,6-tetrafluoropyridine in the transformation did not hamper the efficiency of the process, which generated pyrrolo[1,2-*a*]quinoline **3h** in 86% yield. Additionally, we found that the reaction of 1-[2-(2,2-dibromoethenyl)phenyl]-1*H*-indoles with polyfluoroarenes **2** proceeded smoothly, giving rise to the 4-polyfluoroaryl indolo[1,2-*a*]quinolines **3l–3o** in good yields. The reaction of 1-[2-(2,2-dibromoethenyl)phenyl]-1*H*-pyrrole **1a** with perfluoroarene **2a** in a 10 mmol scale was performed in the meantime, which afforded the corresponding product **3a** in 88% yield.

In conclusion, we have described a novel route for the efficient assembly of 4-polyfluoroaryl pyrrolo[1,2-*a*]quinolines and their derivatives *via* a palladium-catalyzed reaction of

Table 2 Generation of 4-polyfluoroaryl pyrrolo[1,2-*a*]quinolines *via* a palladium-catalyzed reaction of 1-[2-(2,2-dibromoethenyl)phenyl]-1*H*-pyrrole with polyfluoroarene[a]





[a] Isolated yield based on 1-(2-(2,2-dibromovinyl)phenyl)-1*H*-pyrrole **1**.

1-[2-(2,2-dibromoethenyl)phenyl]-1*H*-pyrroles with polyfluoroarenes. This transformation incorporates an intermolecular alkenylation of a polyfluoroarene C–H bond and an intramolecular alkenylation of a pyrrole or indole C–H bond in one step.

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13 General experimental procedure for the palladium-catalyzed reaction of 1-[2-(2,2-dibromoethenyl)phenyl]-1*H*-pyrrole **1** with polyfluoroarene **2**: polyfluoroarene **2** was added to a solution of 1-(2-(2,2-dibromovinyl)phenyl)-1*H*-pyrrole **1** (0.4 mmol), $Pd(OAc)_2$ (5 mol%), Ru-Phos (10 mol%), and Cs_2CO_3 (3.0 equiv.) in toluene (2.0 mL). The mixture was stirred at 90 °C for 12 hours. After completion of the reaction as indicated by TLC, the residue was purified directly by flash chromatography on silica gel to afford products **3**. For details, please see the ESI†.

