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A Foldamer-Based Organocatalyst for Direct Arylations of Unactivated Arenes

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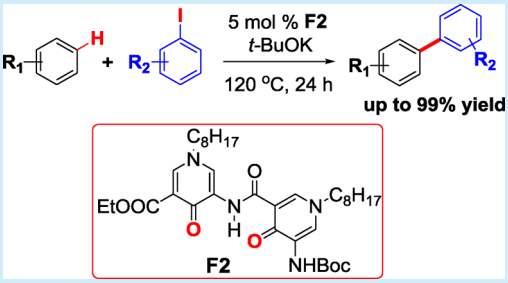
Supporting Information

ABSTRACT: It was demonstrated that a simple yet well-folded pyridone dimer, possessing two convergently aligned electron-rich O atoms for potassium binding, can serve as a highly efficient organocatalyst for catalyzing transition-metal-free arylations of unactivated aromatic C−H bonds with aryl halides in the presence of *t*-BuOK. A wide range of aryl iodides could be cross-coupled with unactivated arenes in moderate to excellent yields. The experiments using radical-scavenging reagents confirm the participation of radicals in this catalytic transformation.



Organocatalysts as an efficient alternative to transition-metal-based catalysts have attracted increasing attention and interest from synthetic chemists. Using these greener catalysts,[1] expensive transition metals and other organometallic reagents can be avoided while providing a strategic solution to construct pharmaceutically relevant molecular scaffolds, including biaryls that could serve as important moieties in the synthesis of pharmaceuticals, natural products, agrochemicals, and functional materials.[2] It is now believed that the potassium *tert*-butoxide mediated catalytic arylation reactions, leading to biaryl molecules, involve aryl radicals produced via a single-electron transfer (SET) process, which is initiated by the interaction of organocatalysts with *t*-BuOK.[1]

H-bonded aromatic foldamers constitute a rich family of structurally diverse folding molecules with a rigid conformation and versatile functions.[3] In particular, over recent years, our group has demonstrated a wide range of interesting functions, including molecular recognition of small molecules,[4a−c] ions[4d,i] and water,[4m] solvent gelation,[4n] reactive sieving,[4o,p] and water transport across cell membranes.[4l] However, aromatic foldamers have rarely been used in organic reactions as the catalysts. We recently reported such a first example, i.e., a macrocyclic H-bonded aromatic pentamer (**P5b**) made up of five pyridone motifs that could efficiently catalyze direct arylations of unactivated arenes (Figure 1a).[1k] This pentamer contains an appropriately sized interior cavity of 1.4 Å in radius that is decorated by five carbonyl O atoms, and can bind many metal ions including the K^+ ion.[4f]

Very recently, we found that acyclic pyridone-based aromatic foldamers (**F1**−**F5**, Figure 1a) fold into crescent-shaped structures to enclose a slightly enlarged interior cavity of ∼1.6 Å in radius. Interestingly, these acyclic foldamer molecules also exhibit good binding toward the K^+ ion.[5] Given the similarities in structure and in potassium binding between cyclic **P5b** and acyclic **F1**−**F5**, we believed **F1**−**F5** might be capable of performing similar catalytic functions. We therefore decided to investigate the possible use of these acyclic foldamers to catalyze direct arylations of unactivated arenes with aryl halides in the absence of transition metals.

The simplest arylation reaction between 4-iodoanisole (**1a**) and benzene (**2a**) was used to gauge the catalytic potential of foldamer-based catalysts (**F1**−**F5**) using the standard conditions involving 3 equiv of *t*-BuOK at 100 °C for 24 h. With respect to the control experiment that generated no desired product **3a** in the absence of catalysts (entry 1, Table 1), a loading of 20 mol % of **F1**−**F5** invariably produced **3a** with **F2** giving the highest yield of 76% (entries 2−6, Table 1). Although we are not sure why **F2** acts as the best catalyst among **F1**−**F5**, the ability of these folding molecules to catalyze the direct arylation should arise from their ability to bind the K^+ ion, enabling s single-electron transfer process to take place. We then further investigated the reactions using different bases (e.g., *t*-BuOLi, *t*-BuONa, and KOH) and found that no product could be obtained under the same conditions using **F2** as the catalyst (entries 7−9, Table 1). Given the fact that **F2** binds K^+ more strongly than Na^+ or Li^+,[5] these results indicate that a stronger base (*t*-BuO^- vs OH^-) and availability of such a base (e.g., *t*-BuO^-) in solution via potassium chelation by the ligand are critically important to drive the reaction to completion.

Similar to **P5b**,[1k] a higher catalyst loading of **F2** does not lead to a higher catalytic efficiency, which is contradictory to many other types of organocatalysts. Instead, the highest catalytic

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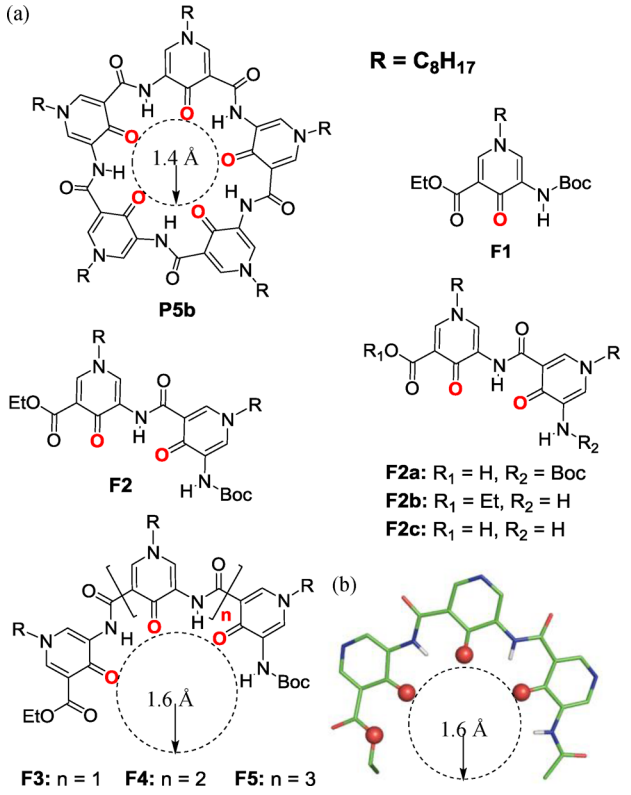
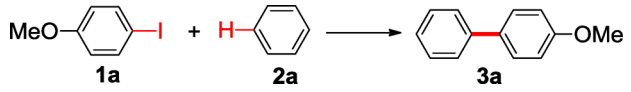


Figure 1. (a) Chemical structures of aromatic foldamers **P5b** and **F1**–**F5** and (b) crystal structure of a trimer molecule containing three pyridone units.[4g]

yield of 84% was achieved with the use of 5 mol % loading of **F2** (entries 3 and 10 vs entry 11, Table 1), likely due to the weakened $\pi-\pi$ stacking among aromatic molecules at lower concentrations. Increasing the reaction time from 24 to 48 h (entry 12, Table 1) or temperature from 100 to 120 °C (entry 13, Table 1) resulted in complete conversions with isolated yields of 95% and 96%, respectively. Additional investigations using a lesser amount of base (entry 14, Table 1) or catalyst (entry 15, Table 1) show that 3 equiv of *t*-BuOK and 5 mol % of **F2** are necessary for achieving optimum catalytic efficiency. Under these optimized conditions, oxygen-rich 18-crown-6 only gave a 25% yield. Using these optimized conditions, we also have tested three analogs of **F2**, i.e., **F2a**–**F2c** that contain COOH or NH_2 at the ends, together with **F1** and **F3**–**F5**. Except for **F1** that is not very stable at 120 °C under the basic conditions (entry 19, Table 1), all the others gave rise to excellent yields (entries 16–22, Table 1), albeit slightly worse than **F2**. In view of its structural simplicity and ease in synthesis, **F2** was employed in all subsequent arylation reactions.

To examine the generality of the optimized catalytic system toward substrates of various types, we surveyed a range of aryl iodides as well as bromides/chloride of limited types (Table 2). The direct arylation reactions of benzene with various aryl iodides including those bearing electron-donating or -withdrawing groups proceeded readily with yields ranging from 71% to 97% (entries 1–9, Table 2). Notably, a high yield of 89% could be obtained when sterically hindered 2-iodoanisole (**1c**) was used in the reaction (entry 3, Table 2). While a mixture containing desired **3h** in high yield of 85% and byproduct of *p*-terphenyl in 10% yield was obtained for 1-fluoro-4-iodobenzene carrying two possibly reactive functional groups (**1h**, entry 8,

Table 1. Optimization of Arylation Conditions[a]



1a 2a 3a

entry	catalyst (equiv)	base (equiv)	temp (°C)	yield (%)[b]
1	–	*t*-BuOK (3.0)	100	0
2	**F1** (0.2)	*t*-BuOK (3.0)	100	64
3	**F2** (0.2)	*t*-BuOK (3.0)	100	76
4	**F3** (0.2)	*t*-BuOK (3.0)	100	25
5	**F4** (0.2)	*t*-BuOK (3.0)	100	42
6	**F5** (0.2)	*t*-BuOK (3.0)	100	5
7	**F2** (0.2)	*t*-BuOLi (3.0)	100	0
8	**F2** (0.2)	*t*-BuONa (3.0)	100	0
9	**F2** (0.2)	KOH (3.0)	100	0
10	**F2** (0.1)	*t*-BuOK (3.0)	100	75
11	**F2** (0.05)	*t*-BuOK (3.0)	100	84
12[c,d]	**F2** (0.05)	*t*-BuOK (3.0)	100	99 (95)
13[c]	**F2** (0.05)	*t*-BuOK (3.0)	120	99 (96)
14	**F2** (0.05)	*t*-BuOK (2.0)	120	51
15	**F2** (0.02)	*t*-BuOK (3.0)	120	80
16	**F2a** (0.05)	*t*-BuOK (3.0)	120	92
17	**F2b** (0.05)	*t*-BuOK (3.0)	120	93
18	**F2c** (0.05)	*t*-BuOK (3.0)	120	93
19	**F1** (0.05)	*t*-BuOK (3.0)	120	25
20	**F3** (0.05)	*t*-BuOK (3.0)	120	91
21	**F4** (0.05)	*t*-BuOK (3.0)	120	86
22	**F5** (0.05)	*t*-BuOK (3.0)	120	92

[a]Reaction conditions: 4-iodoanisole (0.2 mmol), benzene (3 mL), base, and catalyst in a sealed Schlenk tube, 24 h. [b]Yields were determined by NMR analysis. [c]Isolated yield in parentheses. [d]Reaction time: 48 h.

Table 2), use of 1-chloro-4-iodobenzene (**1i**, entry 9, Table 2) led to a mixture of 4-chlorobiphenyl, which is the expected product, and *p*-terphenyl, both at low yield (data not shown). Nevertheless, increasing *t*-BuOK from 3 to 5 equiv generated *p*-terphenyl as the only product with an 85% yield (entry 9, Table 2). This is interesting since simple chlorobenzene is unreactive under the coupling conditions (entry 14, Table 2). Naphthyl and thienyl iodides also underwent coupling reactions with benzene in good yields (entries 10 and 11, Table 2). Further testing showed that aryl bromides expectedly reacted more slowly than aryl iodides with lower yields (entries 12 and 13, Table 2).

This foldamer-based catalytic protocol for C–H bond activation was further applied to a series of arenes. Reactions of **1a** with monosubstituted arenes bearing either electron-donating or -withdrawing groups such as **2b**–**2d** yielded a mixture of regioisomers in which the *ortho*-isomers always predominated (entries 1–3, Table 3), and arylations seem to favor electron-deficient arenes (entries 1 and 2 vs 3, Table 3). When disubstituted arenes, i.e., *p*-xylene (**2e**) and 1,4-difluorobenzene (**2f**), were used in the reaction, the desired products were produced with 41% and 51% yields, respectively (entries 4 and 5, Table 3).

Involvement of radicals in this type of arylation reactions has been proposed with experimental support from early investigations.[1] Consistent with this mechanism and for **F2**-catalyzed arylation reactions, addition of 1 equiv of radical scavengers of either TEMPO (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl) or 1,1-diphenylethelene into the reaction indeed completely aborted the arylations, and no desired products

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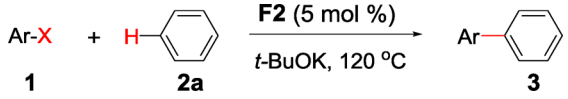
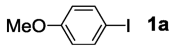
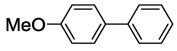
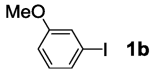
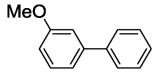
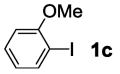
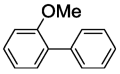
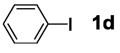
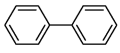
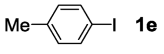
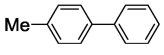
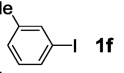
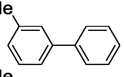
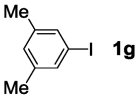
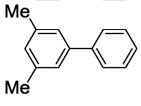
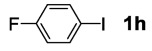
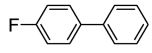
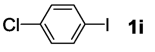
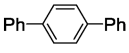
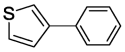
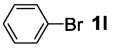
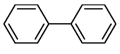
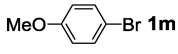
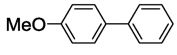
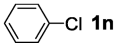
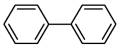
Table 2. Direct Arylation Reactions of Benzene with Aryl Halides[a]



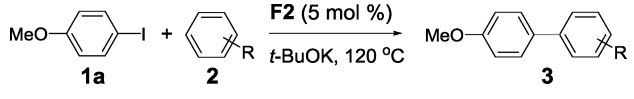
entry	halide (**1**)	product (**3**)	yield (%)[b]
1	 **1a**	 **3a**	96 (93[c])
2	 **1b**	 **3b**	86
3	 **1c**	 **3c**	89
4	 **1d**	 **3d**	97
5	 **1e**	 **3e**	86
6	 **1f**	 **3f**	90
7	 **1g**	 **3g**	71
8[d]	 **1h**	 **3h**	85
9[e]	 **1i**	 **3i**	85
10	 **1j**	 **3j**	66
11	 **1k**	 **3k**	63
12[f]	 **1l**	 **3d**	60
13	 **1m**	 **3a**	57
14	 **1n**	 **3d**	0

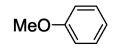
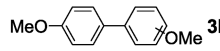
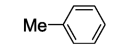
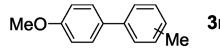
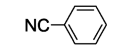
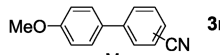
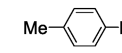
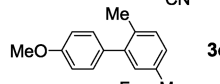
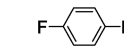
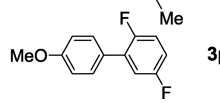
[a]Reaction conditions: Ar−X (0.2 mmol), *t*-BuOK (3 equiv), **F2** (5 mol %), and benzene (3 mL) in a sealed Schlenk tube, 120 °C, 24 h. [b]Isolated yields. [c]**1a** at the 1.0 mmol scale. [d]10% *p*-terphenyl was isolated. [e]5 equiv of *t*-BuOK were used. [f]48 h.

were observed (entries 1 and 2, Table 4). A kinetic isotope experiment involving **1a** reacting with an equal molar mixture of benzene and deuterated-benzene yielded 1.09 for the value of $k_{H/D}$, suggesting that cleavage of the aromatic C−H bond does not constitute a rate-limiting step in the arylation (Scheme 1).

Based on the above observations and recent reports by others,[1,2e,6] a radical-mediated catalytic mechanism can be proposed as shown in Scheme 2. The catalytic cycle is initiated by encapsulating potassium *tert*-butoxide in the cavity of **F2** via the formation of two strong K^+−O coordination bonds. This complex then transfers one electron to the aryl halide, which undergoes one-electron reduction to produce the aryl radical anion after C−X bond cleavage. The generated radical anion adds to benzene to form a biaryl radical intermediate from which the biaryl radical anion was generated after deprotonation by potassium *tert*-butoxide. Subsequent reaction involving

Table 3. Direct Arylation Reactions of Aryl Iodides with Arenes[a]



entry	arene (**2**)	product (**3**)	yield (%)[b]	o/m/p ratio[c]
1	 **2b**	 **3l**	50	1.0/0.56/0.33
2	 **2c**	 **3m**	47	1.0/0.53/0.32
3	 **2d**	 **3n**	73	1.0/0.39/0.17
4	 **2e**	 **3o**	41	
5	 **2f**	 **3p**	51	

[a]Reaction conditions: Ar−X (0.2 mmol), *t*-BuOK (3 equiv), **F2** (5 mol %), and arenes (2 mL) in sealed Schlenk tube, 120 °C, 24 h. [b]Isolated yields. [c]Ratio of products determined by NMR analysis.

Table 4. Participation of Radicals in Arylation Reactions

entry	additive (equiv)	yield (%)[a]
1	TEMPO (1.0)	0
2	1,1-diyldibenzene (1.0)	0
3	no radical scavenger	99

[a]Yields determined by ^{1}H NMR.

Scheme 1. Kinetic Isotope Effect Experiment

Scheme 2. A Possible Catalytic Cycle

this radical anion and an aryl halide through a single electron transfer affords the product as well as aryl radical that enables the catalysis to continue to the next catalytic cycle.

In conclusion, we have demonstrated here a novel foldamer-based organocatalyst **F2** for efficient construction of biaryl compounds using transition-metal-free direct arylations of

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unactivated arenes with haloarenes in the presence of potassium *tert*-butoxide. Good to excellent yields can be obtained for a wide range of aryl iodides. One significant and advantageous feature of this new catalytic system lies in its low catalyst loading of 5 mol %, especially in comparison with the catalyst loadings of 10 to 40 mol % required for all organocatalyts developed by others for the same type of arylation reactions.[1] We believe this simple easily accessible organocatalyst might find interesting uses in constructing pharmaceutically important biaryl scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00921.

Synthetic procedures and characterizations (^{1}H and ^{13}C NMR) for arylation products (PDF)

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Notes

The authors declare no competing financial interest.

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