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A macrocyclic aromatic pyridone pentamer as a highly efficient organocatalyst for the direct arylations of unactivated arenes†

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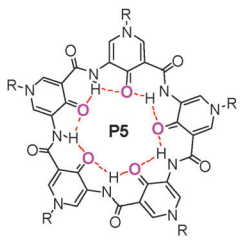
A macrocyclic aromatic pyridone pentamer was shown to catalyze highly efficient transition-metal-free arylations of unactivated aromatic C–H bonds with aryl iodides and bromides in the presence of potassium *tert*-butoxide.

Biaryl is a pivotal scaffold in the synthesis of pharmaceuticals, natural products, agrochemicals and functional materials.[1] Over the past decades, various strategies have been developed, the prevailing methods of which are the transition-metal-catalyzed cross-coupling reactions of organometallic reagents with haloarenes.[2] However, these methods not only suffer from sensitive organometallic reagents and expensive metal catalysts, but also often produce undesired, toxic and stoichiometric side products. As an efficient and green alternative to transition-metal-catalyzed reactions, organocatalysts attract more and more attention from the synthetic chemists, providing a strategic solution to assemble diverse molecules. A very recent development involves generating biaryl molecules with the use of organocatalysts interacting with *tert*-butoxide (*t*-BuO$^-$) to initiate the aryl radicals *via* the single-electron transfer (SET) that subsequently promote the direct arylations of unactivated arenes.[3]

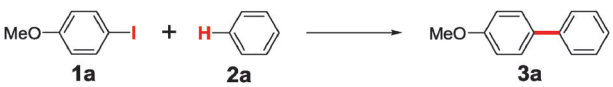
Aromatic foldamers with backbones rigidified by H-bonds have been the subject of intense attention over recent years, due to their versatile properties and potential applications including molecular recognition,[4] ion channels,[5] and differential binding of alkaline metal ions.[6] Aromatic foldamers, however, have been rarely applied as organocatalysts for chemical transformations. Recently, we reported a novel class of H-bonded macrocyclic aromatic pentamers (**P5**) made up of five pyridone motifs that enclose an appropriately sized interior decorated with five carbonyl O-atoms to display tight binding of 10^8 M^{-1} in the water–$CHCl_3$ system toward alkali metal ions.[6b,c] Inspired by the recent elegant works on the use of organocatalysts to promote transition-metal-free arylation reactions,[3] we speculated that macrocyclic ion-binding pentamers **P5** could also serve as efficient catalysts for the direct arylations of the inert aromatic C–H bonds with aryl halides in the absence of transition metals. To the best of our knowledge, there has been no related report using the backbone-rigidified folding molecules such as **P5**[7] as the organocatalysts in the transition-metal-free cross-coupling reactions.



P5a: R = C_8H_{17}
P5b: R = Bn
P5c: R = *i*-Bu
P5d: R = CH_2CH_2OEt

The cross-coupling reaction of 4-iodoanisole (**1a**) with benzene (**2a**) was chosen as the model reaction for optimizing the reaction conditions. A control experiment was firstly performed with the use of 3.0 equivalents of KO*t*-Bu at 120 °C but without the use of any catalyst, and

Table 1 Optimization of arylation reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst (equiv.)	Base (equiv.)	*T* (°C)	*t* (h)	Yield[b] (%)
1	**P5a** (0.00)	KO*t*-Bu (3.0)	120	24	8
2	**P5a** (0.05)	KO*t*-Bu (3.0)	120	24	95
3	**P5a** (0.05)	NaO*t*-Bu (3.0)	120	24	3
4	**P5a** (0.05)	LiO*t*-Bu (3.0)	120	24	0
5	**P5a** (0.05)	KOH (3.0)	120	24	2
6	**P5a** (0.05)	K_3PO_4 (3.0)	120	24	0
7	**P5a** (0.03)	KO*t*-Bu (3.0)	120	24	99 (96)
8	**P5a** (0.02)	KO*t*-Bu (3.0)	120	24	99 (96)
9	**P5a** (0.01)	KO*t*-Bu (3.0)	120	24	56
10	**P5a** (0.02)	KO*t*-Bu (2.0)	120	24	53
11	**P5a** (0.02)	KO*t*-Bu (3.0)	110	24	74
12	**P5a** (0.02)	KO*t*-Bu (3.0)	120	20	85
13	**P5b** (0.02)	KO*t*-Bu (3.0)	120	24	14
14	**P5c** (0.02)	KO*t*-Bu (3.0)	120	24	49
15	**P5d** (0.02)	KO*t*-Bu (3.0)	120	24	42

[a] **1a** (0.2 mmol), base, catalyst and benzene (3 mL) in a sealed Schlenk tube. [b] Yields were determined by ^{1}H NMR (isolated yield in parentheses).

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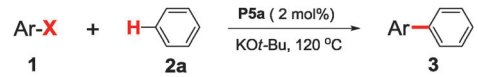
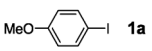
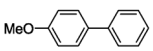
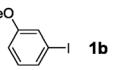
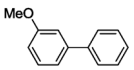
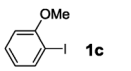
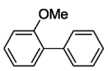
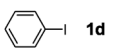
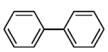
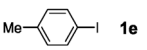
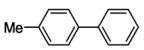
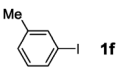
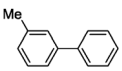
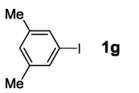
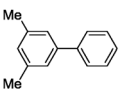
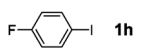
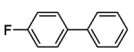
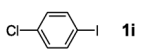
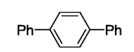
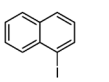
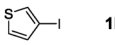
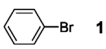
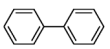
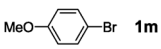
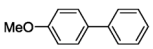
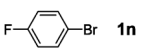
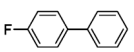
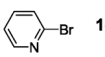
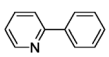
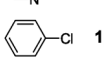
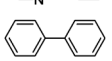
† Electronic supplementary information (ESI) available: The details of experiments and a full set of characterization data including ^{1}H, ^{13}C NMR and HRMS. See DOI: 10.1039/c3cc00019b

the desired product was obtained with 8% yield (Table 1, entry 1). In sharp contrast, 95% yield can be obtained with the use of 5 mol% of **P5a** (Table 1, entry 2). Various bases such as NaO*t*-Bu, LiO*t*-Bu, KOH and K_3PO_4 were then tested, giving rise to either no product or very low yields (Table 1, entries 3–6). Surprisingly, a reduction in catalyst loading from 5 to 3 and further to 2 mol% led to very clean reactions with 96% isolated yield in both cases (Table 1, entries 7 and 8).[8a] A catalyst loading as low as 2 mol% is quite significant since all the hitherto reported organocatalysts for catalyzing the same arylation reactions require from 10 to 40 mol% catalyst loadings.[3,8b] After screening various factors (*e.g.*, amount of base, temperature and reaction time; Table 1, entries 9–12), the best conditions for promoting the arylations involve the use of 2 mol% of **P5a** and 3 equivalents of KO*t*-Bu at 120 °C for 24 h. An additional testing of other analogous macrocycles **P5c** and **P5d**, which differ from **P5a** by their exterior side chains, reveals **P5a** to be the best catalyst (Table 1, entries 13–15).

Table 2 Direct arylations of benzene with aryl halides[a]



1 2a 3

Entry	Ar group	Product	Yield (%)
1	 1a	 3a	96
2	 1b	 3b	83
3	 1c	 3c	94
4	 1d	 3d	98
5	 1e	 3e	89
6	 1f	 3f	92
7	 1g	 3g	84
8[b]	 1h	 3h	80
9[c]	 1i	 3i	94
10	 1j	 3j	75
11	 1k	 3k	86
12[d]	 1l	 3d	80
13[d]	 1m	 3a	60
14[e]	 1n	 3h	25
15	 1o	 3l	90
16	 1p	 3d	0

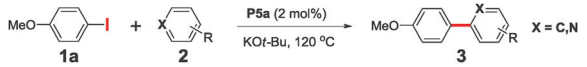
[a] Ar–X **1** (0.2 mmol), KO*t*-Bu (3 equiv.), **P5a** (2 mol%) and benzene (3 mL) in a sealed Schlenk tube, 120 °C, 24 h, isolated yields. [b] 15% *p*-terphenyl **3i** was isolated. [c] 5 equiv. of KO*t*-Bu was used. [d] Reaction time: 48 h. [e] 17% *p*-terphenyl **3i** was isolated.

With the optimal conditions in hand, we investigated the arylations of benzene with a range of aryl halides. Simple iodobenzene **1d** and other aryl iodides bearing electron-donating or withdrawing groups can be efficiently coupled with benzene to produce the desired products in high yields of 83–98% (Table 2, entries 1–9). Notably, sterically hindered aryl iodides **1c** and **1j** gave isolated yields of 94% and 75%, respectively (Table 2, entries 3 and 10). Interestingly, arylation using dihalide **1h** additionally produced *p*-terphenyl **3i** as the by-product in 15% yield (Table 2, entry 8), and **1i** largely underwent double phenylation to afford **3i** as the major product in 94% yield with the use of 5 rather than 3 equivalents of *t*-BuOK (Table 2, entry 9). While this newly discovered catalyst can be used to promote the arylation of aryl bromides under either optimized conditions or a longer reaction time, producing the desired biaryl products in 25–90% (Table 2, entries 12 and 13), aryl chlorides such as chlorobenzene **1p** were unreactive under the identical conditions (Table 2, entry 16).

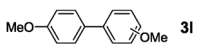
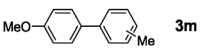
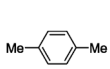
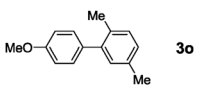
The substrate scope and regioselectivities in arylations were further explored on the different arenes. Reactions of **1a** with substituted benzenes invariably afforded regioisomeric mixtures with a high *ortho* ratio (Table 3, entries 1, 2, 5 and 6). The arenes with electron-withdrawing groups (Table 3, entries 4–6) coupled with **1a** more efficiently than those carrying electron-donating groups (Table 3, entries 1–3), highlighting the importance of the relative acidity of aromatic C–H bonds in the arylation reactions and suggesting the **P5a**-mediated direct arylation of aromatic C–H bonds to proceed by homolytic aromatic substitution with aryl radicals[3c] that differs from the typical transition-metal-catalyzed reactions.

Consistent with the involvement of aryl radicals in the arylation reactions promoted by macrocycle **P5a**, addition of one equivalent of free radical scavengers of either TEMPO or 1,1-diphenylethelene put the reaction to a complete stop and no desired product could be obtained (Table 4). These results contrast well with 99% yield obtained without the use of radical scavengers (Table 1, entry 8). An additional kinetic isotope experiment yielded a k_H/k_D value of 1.09 (Scheme 1), demonstrating that the cleavage of the aromatic C–H bond is not the rate-limiting step in the arylation reaction.

Table 3 Direct arylations of aryl iodide with arenes[a]

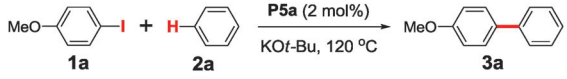


1a 2 3

Entry	Arenes	Product	Yield (%)	Ratio of *o*/*m*/*p*[b]
1	 2b	 3l	60	1.0/0.23/0.21
2	 2c	 3m	50	1.0/0.44/0.38
3	 2d	 3o	44	
4	2e	3p	65	
5	2f	3n	79	1.0/0.48/0.37
6	2g	3q	85	1.0/0.76/0.32

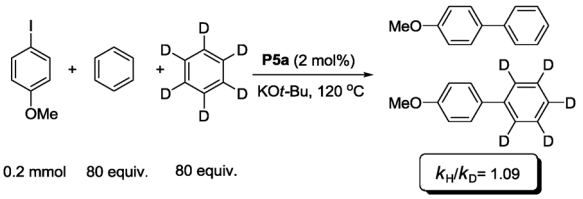
[a] **1a** (0.2 mmol), KO*t*-Bu (3 equiv.), **P5a** (2 mol%) and arenes **2** (2 mL) in a sealed Schlenk tube, 120 °C, 48 h, isolated yields. [b] Ratio of products determined by ^{1}H NMR analysis.

Table 4 Arylation reactions with radical scavengers

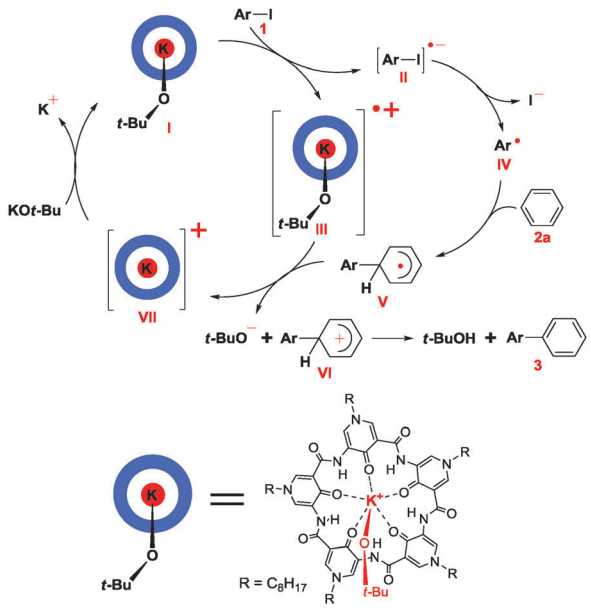


Entry	Additive (equiv.)	Yield of **3a**[a] (%)
1	TEMPO (1.0)	0
2	Diyldibenzene (1.0)	0

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



Scheme 1 Kinetic isotope effect.



Scheme 2 The proposed catalytic cycle of arylation reactions.

On the basis of the above data and related results reported by others,[3,9] a radical-mediated catalytic mechanism is very likely as illustrated in Scheme 2. In the proposed catalytic cycle, the cation-binding macrocycle **P5a** encapsulates the K^+ inside its cavity and forms the complex **I**, which subsequently transfers a single electron to iodobenzene **1**, yielding the intermediate radical anion **II** and cation **III**. From **II**, aromatic radical **IV** is formed that adds to benzene **2a** to generate biaryl radical **V**. Oxidation of **V** by **III** produces cations **VI** and **VII** of which **VI** is deprotonated by a *t*-butoxide anion generated *in situ* to afford cross-coupled product **3**, and **VII** reacts with KO*t*-Bu to re-generate complex **I** that allows the catalytic cycle to continue.

In summary, we disclose here a novel foldamer-based H-bond-rigidified organocatalyst **P5a**,[7] enabling the efficient construction of biaryls *via* direct arylations of unactivated arenes with iodoarenes and bromoarenes in the presence of KO*t*-Bu by using as low as 2 mol% catalyst loading in a transition-metal-free fashion. Very good to excellent yields were obtained for broad substrates. **P5a** thus represents one of the most efficient additions into the toolbox, currently with a limited collection of organocatalysts for radical-mediated coupling reactions. **P5a** may, further, hold promise in producing other types of molecular skeletons *via* reactions where radicals play an important role.[9a]

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8 (*a*) Lowering down the concentration of **P5a** likely discourages the self-aggregation and increases the effective concentration of monomeric macrocycles for them to efficiently interact with KO*t*-Bu to promote better arylation reactions; (*b*) Such a low catalyst loading may arise from the likelihood that the planar and electron-rich nature of the macrocyclic backbone in **P5a** greatly facilitates the initial stage involving the endothermic formation of high energy intermediate species **I** and subsequent reduction of the aryl halide by *t*-butoxide as proposed in Scheme 2. Of further interest to note is that 18-crown-6 gave 25% yield under the optimized conditions used for **P5a**.
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