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COMMUNICATION

K-bis(2-ethylhexyl) phosphate (BEHPK): a novel additive for C-H arylation†

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A Ru-mediated highly efficient direct C-H arylation of α -heteroaromatic benzenes has been accomplished by addition of readily accessible K-bis(2-ethylhexyl) phosphate (BEHPK), which allowed a facile and economical access to a wide range of functionalized biaryls including active pharmaceutical ingredients.

Inspired by conceptually high atom economy, Ru-catalyzed C-H arylation has aroused a keen interest in the synthesis of biaryls (Figure 1).¹ The approach does not need any activating group such as boronic acid to effect the C(sp²)-C(sp²) coupling. However, most of the protocols hitherto reported required high Ru catalyst loading (5 to 10 mol%) and often suffered from lack of reproducibility in large scale synthesis.² During our process development of angiotensin II receptor blockers (ARBs) using C-H arylation,³ same kind of issues have arisen in the reaction of 1-benzyl-2-phenyl-1*H*-tetrazole (**1**) with 4-bromobenzyl acetate (**2**) whose product **3** is a key common intermediate for ARBs (Table 1, Entry 1).³ It seriously retarded further development to multi-hundred kilogram scale commercial production using the new approach. To address the challenge, we searched for a better catalytic system with a new additive to ensure robustness of the C-H arylation in scale. Disclosed herein is a highly efficient and practical protocol for the C-H arylation employing a novel additive, K-bis(2-ethylhexyl) phosphate (BEHPK).

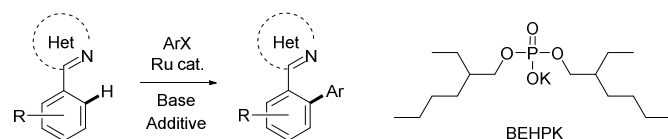
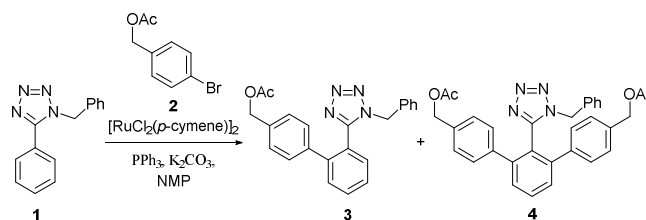
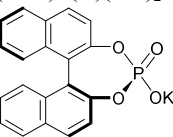


Figure 1. Direct C-H arylation of arenes.

Lack of reproducibility in the Ru-catalyzed C-H arylation has been reported by Merck in the synthesis of Anacetrapib.² They analysed a trace amount of impurities in the reaction system and eventually found addition of a carboxylic acid salt (AcOK⁴) was effective to

Table 1 Screen of an additive for C-H arylation of 1-benzyl-2-phenyl-1*H*-tetrazole (**1**) with 4-bromobenzyl acetate (**2**)^a



Entry	Additive	3/4 ^b	Conv ^b (%)	Yield ^c (%)
1	none	- ^d	0-86	0-80
2 ^e	AcOK	89/11	51	39
3	AcOK	89/11	80	71
4	PivOK	86/14	71	64
5	K-Adamantanecarboxylate	88/12	78	77
6	K-Mesitylenecarboxylate	88/12	67	62
7	(EtO) ₂ P(O)(OK)	94/6	62	56
8	(BuO) ₂ P(O)(OK)	97/3	34	25
9	(BuO)P(O)(OK) ₂	96/4	40	29
10		97/3	25	16
11	(PhO) ₂ P(O)(OK)	93/7	66	60
12	(2-Et-HexO)₂P(O)(OK) (BEHPK)	95/5	87	82

^a Reactions were conducted by employing **1** (2.0 g, 8.46 mmol), **2** (2.13 g, 9.31 mmol, 1.1 equiv), [RuCl₂(*p*-cymene)]₂ (26 mg, 0.0423 mmol, 0.5 mol%), PPh₃ (44 mg, 0.168 mmol, 2.0 equiv to Ru), additive (0.168 mmol, 2.0 equiv to Ru), K₂CO₃ (1.17 g, 8.46 mmol, 1.0 equiv) in NMP (10 mL) at 138°C for 6 h. ^b Determined by HPLC. ^c Assay yield. ^d Not determined. ^e PPh₃ (22 mg, 0.084 mmol, 1.0 equiv to Ru) was employed.

make the reaction reproducible. Hence, we first tested AcOK as an additive for the C-H arylation. The reaction was conducted by stirring a mixture of **1** and **2** in the presence of $[\text{RuCl}_2(p\text{-cymene})]_2$ (0.5 mol%) and PPh_3 (1.0 equiv to Ru) and K_2CO_3 in NMP at 138°C for 6 h. A poor yield was obtained and ratio of desired monoarylation product **3** was moderate due to considerable formation of diarylation product **4** ($3/4 = 89/11$, 39% yield, Table 1, Entry 1). To improve the yield the amount of PPh_3 was doubled (2.0 equiv to Ru). Although a better yield was obtained, selectivity of the monoarylation was not improved ($3/4 = 89/11$, 71% yield, Table 1, Entry 2). Use of other well documented carboxylates for the C-H arylation such PivOK^5 , K-adamantanecarboxylate⁶ and K-mesitylenecarboxylate⁶ was similarly accompanied by appreciable magnitude of diarylation product **4** ($3/4 = 86/14$ to $88/12$, Table 1, Entries 4-6). The diarylation product **4** might be removed by recrystallization. However, if the final product is an active pharmaceutical ingredient (API), to reduce the extent of diarylation is quite significant to confirm high quality of the product by conducting minimum number of purification.⁷ The diarylation product might be carried over to the final stage and contaminate API.

To work out the issue, we came up with an idea employing K-phosphate as the additive. *In situ* generated Ru-phosphate might facilitate removal of C-H hydrogen by Lewis basic P=O oxygen (Figure 2).⁸ Two substituents (R) on the phosphate are able to be modified readily to enhance the basicity of the P=O oxygen by inductive effect and/or to retard the diarylation by steric repulsion.

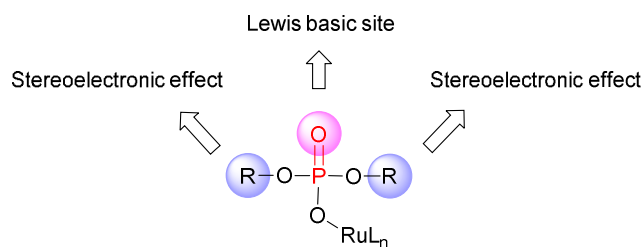


Figure 2 Ru-phosphate as a potential catalyst for C-H arylation

The reaction with a K-phosphate additive was first tested by the use of K-diethyl phosphate. As expected, monoarylation selectivity was much improved but the yield became lower ($3/4 = 94/6$, 56% yield, Table 1, Entry 7). More sterically demanding K-dibutyl phosphate provided a much poorer yield while di-K-monobutyl phosphate gave a similar outcome (25% and 29% yield, respectively, Table 1, Entries 8 and 9). Cyclic K-binaphthyl phosphate⁹ did not improve the yield (16%, Table 1, Entry 10). By using diphenyl phosphate, the yield became higher though still being unsatisfactory (60% yield, Table 1, Entry 11). It should be noted that monoarylation selectivity is high without exception when the phosphates were employed. To improve the yield, a more electronegative aliphatic branched K-bis(2-ethylhexyl) phosphate (BEHPK) was then tested. Gratifyingly, using BEHPK as an additive, a much higher yield was obtained while monoarylation selectivity was retained ($3/4 = 95/5$, 82% yield, Table 1, Entry 12). BEHPK is an inexpensive and widely available chemical and hence readily applicable to commercial large scale production.

Scope of the reaction was tested employing various arenes **5** as the substrate (Table 2). The reaction was conducted in the presence of 2.2 equiv of ArBr **6** and 0.5 mol% of $[\text{RuCl}_2(p\text{-cymene})]_2$. The C-H arylation took place smoothly for 2-phenylpyridine to give arylated product **7** and **8** in good yields though the monoarylation selectivity was poor (Table 2, Entries 1-4). The reaction of 1-phenylpyrazole and 2-phenyloxazoline smoothly provided corresponding arylated

Table 2 C-H arylation of arenes **5** with arylbromides **6**^a

Entry	Arene 5	ArBr 6	7/8	Conv ^b (%)	Yield ^c (%)
1		4-BrPhMe	5/95	100	2 (7) 97 (8)
2		4-BrPhCO ₂ Me	4/96	100	1 (7) 99 (8)
3		4-BrPhCH ₂ OAc	0/100	100	93 (8)
4		4-BrPhCH ₂ OBz	31/69	100	28 (7) 61 (8)
5		4-BrPhMe	21/79	48	10 (7) 38 (8)
6		4-BrPhCO ₂ Me	8/92	100	8 (7) 85 (8)
7		4-BrPhCH ₂ OAc	1/99	100	1 (7) 94 (8)
8		4-BrPhCH ₂ OBz	12/88	91	12 (7) 88 (8)
9		4-BrPhMe	21/30	51	17 (7) 26 (8)
10		4-BrPhCH ₂ OAc	31/69	45	14 (7) 31 (8)
11 ^d		4-BrPhMe	95/5	81	77 (7) 3 (8)
12 ^d		4-BrPhCH ₂ OBz	92/8	77	68 (7) 4 (8)

^a Reactions were conducted by employing **5** (8.46 mmol), **6** (18.6 mmol, 2.2 equiv), $[\text{RuCl}_2(p\text{-cymene})]_2$ (26 mg, 0.0423 mmol, 0.5 mol%), PPh_3 (44 mg, 0.168 mmol, 2.0 equiv to Ru), BEHPK (0.168 mmol, 2.0 equiv to Ru), K_2CO_3 (1.17 g, 8.46 mmol, 1.0 equiv) in NMP (10 mL) at 138°C for 6 h. ^b Determined by HPLC. ^c Assay yield. ^d The amount of bromide **6** is 1.1 equiv.

products as well (Table 2, Entries 5-10). When 1-benzyl-5-phenyl-1H-tetrazole was reacted with 4-bromotoluene or 4-bromobenzyl benzoate, the reaction proceeded well to give the monoarylation product selectively (Table 2, Entries 11 and 12). Although the monoarylation selectivity was not achieved in the reactions except 1-benzyl-5-phenyl-1H-tetrazole as the substrate, fairly good yields were obtained in the presence of quite low Ru catalyst loading (0.5 mol%).¹⁰

In conclusion, BEHPK was found to be highly effective for C-H arylation. It was applied to a practical synthesis of a key common intermediate for ARBs. In the C-H arylation of 1-benzyl-5-phenyl-1H-tetrazole using BEHPK as the additive, higher monoarylation selectivity was achieved to provide the product of much higher purity. Using BEHPK, consistency of the reaction in scale was observed as well.¹¹ Ready availability of BEHPK and ease of operation of the new process would permit a facile access to biaryls of pharmaceutical and commercial importance.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details.

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- 11 The reaction of **1** with 4-bromobenzylbenzoate (Table 2, Entry 15) was successfully conducted with high reproducibility employing 500 g of **1**.