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Efficient Catalytic System for Ru-Catalyzed C−H Arylation and Application to a Practical Synthesis of a Pharmaceutical

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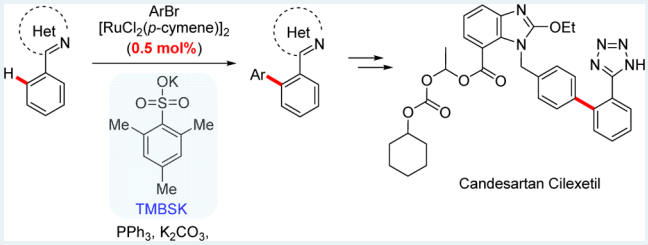
Supporting Information

ABSTRACT: A series of K salts of sulfonic acids have been tested as a cocatalyst for Ru-catalyzed C−H arylation. Among them, K 2, 4, 6-trimethylbenzenesulfonate (TMBSK) was found to be most active, and generality of the reaction was confirmed for a variety of nitrogen-containing heterocycles to give corresponding functionalized biaryls in high yields. The present methodology was applied to a practical synthesis of Candesartan Cilexetil.



KEYWORDS: *C−H activation, direct arylation, ruthenium, sulfonic acids, biaryls, heterocycles*

The Ru-catalyzed C−H arylation reaction has received keen interest as a highly atom-economical approach to prepare biaryl compounds (**1** to **2**, Scheme 1).[1−7] The new approach is able to construct various biaryls of pharmaceutical and material importance without use of any activating group or stoichiometric amount of hazardous organometallic compounds which are required for the conventional cross coupling reactions. The C−H arylation is important not only from a theoretical viewpoint but also from a commercial application, although the use of the methodology is still early in its development in various industries. In order to promote the catalytic system efficiently, the proper choice of a cocatalyst is significant, and extensive research has been conducted to discover the correct catalyst. Among them, K salts of Brønstead acids such as acetic acid,[8,9] pivalic acid,[10,11] adamantanecarboxylic acid,[12] and mesitylenecarboxylic acid[12] have been employed. Very recently, we have disclosed that K bis(2-ethylhexyl)phosphate (BEHPK) exerted high activity in the C−H arylation.[13] However, BEHPK is not completely satisfactory, because the performance is not good for less reactive 2-phenyloxazoline derivatives[13] and bulky substrates such as 1-benzyl-5-phenyl-1*H*-tetrazole and 4-bromobenzyl benzoate (vide infra). Reactivity of the cocatalyst was attributed to a proper ligand excahnge by means of hydrogen bonding.[14] This type of activation might be enhanced by using a stronger acid. Hence, in a search for a better cocatalyst which has higher activity and versatility to compensate for the lack of BEHPK, the author came up with an idea to employ K sulfonate as the cocatalyst whose conjugate acid has a lower pK_a value than the corresponding phosphoric and carboxylic acids (RSO_3H > $RP(O)(OH)_3$ > RCO_2H).[15] Disclosed herein is a novel and highly efficient catalytic system of the C−H arylation which involves 2, 4, 6-trimethylbenzenesulfonate (TMBSK) as a cocatalyst and application of the protocol to a practical of Candesartan Cilexetil (**3**).

In our initial study, the C−H arylation employing K sulfonate as the cocatalyst was tested for the reaction of 1-benzyl-2-phenyl-1*H*-tetrazole (**4**) with 4-bromobenzyl acetate (**5a**) whose product **6a** is a key common intermediate for angiotensin II receptor blockers (ARBs) (Table 1).[13,16−19,23] The reaction was conducted in the presence of [$RuCl_2$(*p*-cymene)]$_2$ (0.5 mol %), PPh_3 (2.0 equiv to Ru), cocatalyst (2.0 equiv to Ru), and K_2CO_3 in NMP at 138 °C for 6 h. The data employing BEHPK is listed for comparison (Table 1, Entry 1).[13] For water content in the reaction mixture, even adding a small amount of water (>2% to NMP) resulted in no conversion. This might be due to generation of 4-bromobenzylalcohol, which considerably retards the reaction.[17] When K methanesulfonate was employed as the cocatalyst, a high monoarylation selectivity similar to BEHPK was obtained, though the yield was declined (**6a**/**7a** = 94/6, 60% yield, Table 1, Entry 2, versus **6a**/**7a** = 95/5, 82% yield, Table 1, Entry 1). The use of aromatic K benzenesulfonate, K *p*-toluenesulfonate, or K *p*-dodecylbenzene- sulfonate did not improve the yield while the monoarylation selectivity was retained (**6a**/**7a** = 94/6−97/3, 28−46% yield, Table 1, Entries 3, 4, and 5). Further screen of the cocatalyst revealed that K 2, 4, 6-trimethylbenzenesulfonate (TMBSK) was found to provide a higher yield which is similar to BEHPK (**6**/**7** = 92/8, 77% yield, Table 1, Entry 6). The amount of PPh_3 in the reaction is significant. Actually the conversion was considerably declined when the amount of PPh_3 was reduced to 1.0 equiv to Ru (18%, Table 1, Entry 7, versus 86%, Table 1, Entry 6). Of particular interest is the result when bulky benzoyl derivative **5b** was employed as the substrate where TMBSK provided a higher yield than BEHPK (80%, Table 1, Entry 9 versus 68%, Table 1, Entry 8).

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Scheme 1. C−H Arylation of Arenes and Candesartan Cilexetil

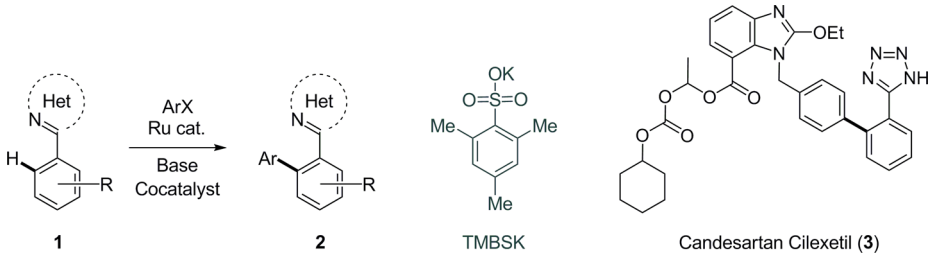
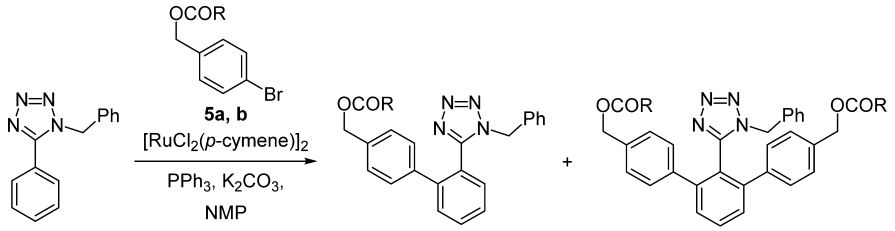


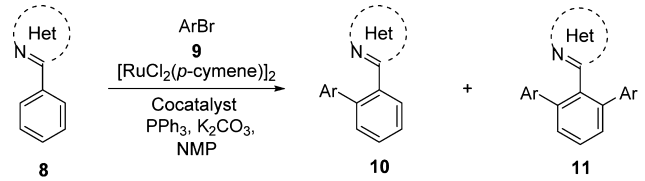
Table 1. Screen of a Cocatalyst for C−H Arylation of 1-Benzyl-2-phenyl-1*H*-tetrazole (4)[a]

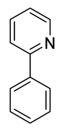
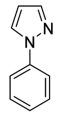
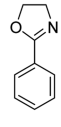


entry	R	cocatalyst	**6**/**7**[b]	conv[b] (%)	yield of **6**[c] (%)
1[5]	Me	Bis(2-Et-HexO)$_2$P(O)OK (BEHPK)	95/5	87	82
2	Me	$MeSO_3K$	94/6	75	60
3	Me	$PhSO_3K$	97/3	35	28
4	Me	4-$MePhSO_3K$	94/6	60	50
5	Me	4-*n*-$C_{12}H_{25}SO_3K$	94/6	59	46
6	Me	2, 4, 6-Me_3PhSO_3K (TMBSK)	92/8	86	77
7[d]	Me	TMBSK	98/2	18	14
8	Ph	BEHPK	92/8	77	68
9	Ph	TMBSK	89/11	83	80

[a]Reactions were conducted by employing **4** (2.0 g, 8.46 mmol), **5** (2.13 g, 9.31 mmol, 1.1 equiv to **4**), $[RuCl_2(p\text{-cymene})]_2$ (26 mg, 0.0423 mmol, 0.5 mol %), PPh_3 (44 mg, 0.168 mmol, 2.0 equiv to Ru), cocatalyst (0.168 mmol, 2.0 equiv to Ru), K_2CO_3 (1.17 g, 8.46 mmol, 1.0 equiv to **4**) in NMP (10 mL) at 138 °C for 6 h. [b]Determined by HPLC. [c]Assay yield. [d]PPh_3 (22 mg, 0.084 mmol, 1.0 equiv to Ru).

Table 2. C−H Arylation of Arenes 8 in the Presence of TMBSK[a]



entry	arene **8**	ArBr **9**	cocatalyst	**10**/**11**	conv[b] (%)	yield of **10** and **11**[c] (%)
1		4-$BrPhCO_2Me$	TMBSK	5/95	100	8, 84
2		4-$BrPhCH_2OBz$	TMBSK	20/80	100	7, 93
3		4-BrPhMe	TMBSK	60/40	100	46, 44
4		4-$BrPhCO_2Me$	TMBSK	5/95	100	5, 93
5		4-$BrPhCH_2OAc$	TMBSK	8/92	100	8, 88
6		4-$BrPhCH_2OBz$	TMBSK	1/99	100	0.3, 99
7		4-$BrPhCH_2OAc$	TMBSK	3/97	100	3, 95
8[13]			BEHPK	31/69	45	14, 31
9		4-$BrPhCH_2OBz$	TMBSK	1/99	100	0.3, 99
10[13]			BEHPK	29/71	50	15, 35

[a]Reactions were conducted by employing **8** (6.44 mmol), **9** (14.2 mmol, 2.2 equiv), $[RuCl_2(p\text{-cymene})]_2$ (20 mg, 0.0322 mmol, 0.5 mol %), PPh_3 (34 mg, 0.129 mmol, 2.0 equiv to Ru), cocatalyst (27 mg, 0.129 mmol, 2.0 equiv to Ru), K_2CO_3 (0.89 g, 6.44 mmol, 1.0 equiv) in NMP (5 mL) at 138 °C for 6 h. For characterization data of **10** and **11**, see ref 13. [b]Determined by HPLC. [c]Assay yield.

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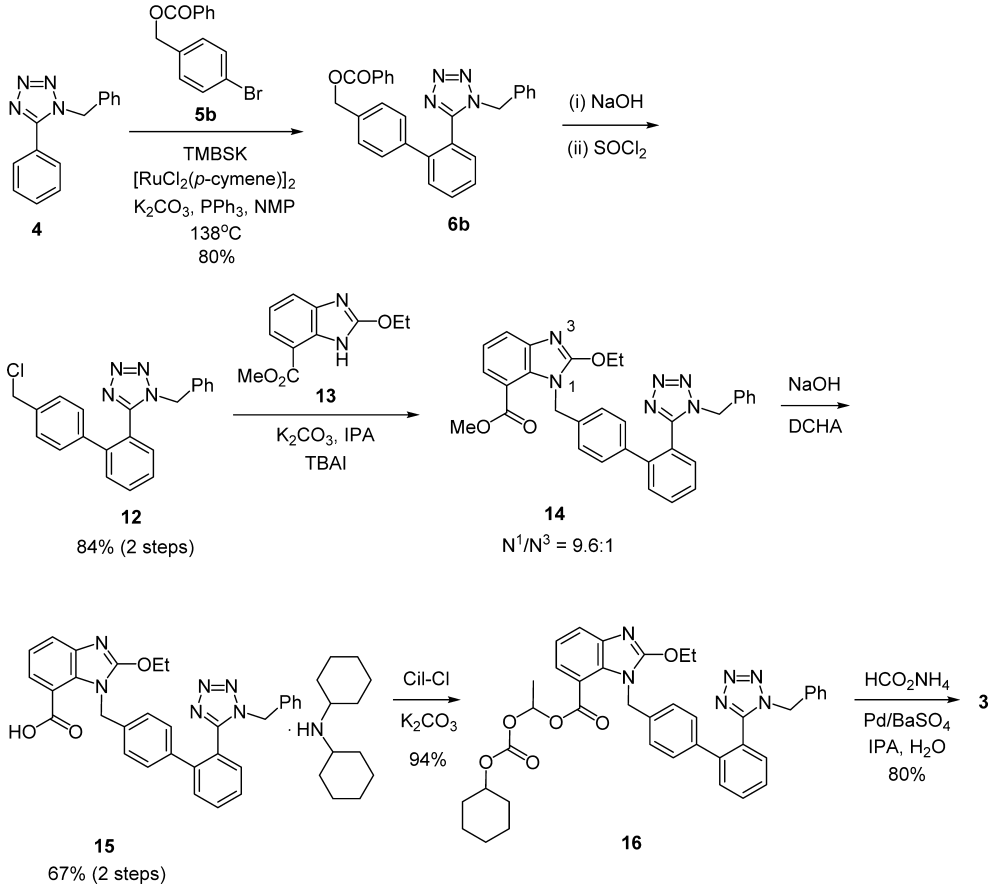
Scheme 2. Synthesis of Candesartan Cilexetil (3)



The benzoyl derivative **6b** has a practical advantage over acetyl derivative **6a** in terms of better crystallinity. It remarkably facilitates the isolation without silica gel column chromatography (vide infra).

The reaction with TMBSK was further tested employing various nitrogen-containing heterocycles, as shown in Table 2. The use of pyridine and pyrazole derivatives provided arylated products in high yields (Table 2, Entries 1–6). It should be noted TMBSK provided oxazoline derivatives in much higher conversions than BEHPK (100%, Table 2, Entries 7 and 9, versus 45% and 50%, Table 2, Entries 8 and 10). Practically, TMBSK, whose corresponding free sulfonic acid is commercially available as a stable dihydrate, is nonhygroscopic, and its handling is much easier than very hygroscopic BEHPK.

The present method was applied to a synthesis of Candesartan Cilexetil (**3**), one of the most potent antihypertension drugs.[20,21] In our previous synthesis of **3**,[18] acetyl derivative **6a** was employed as the intermediate. However, in an improved process, a bezoyl derivative **6b** was chosen as the intermediate, because it has a practical advantage over **6a** on ease of crystallization. Considering the entire route of synthesis of **3**, the previous methods consist of a long linear-type pathway where benzimidazole moiety was formed consecutively in the main reaction sequence.[20,21] To avoid the impracticality,[22] preformed benzimidazole **13** was coupled with a chloride **12**, which was readily prepared from **6b** via debenzoylation and chlorination (Scheme 2). The regioselectivity of the alkylation of **13** with **12** is significant because undesired N^3-alkyl derivative might be formed and carried over to the final active pharmaceutical ingredient (API). When the reaction was conducted in DMF, a poor selectivity was obtained (N^1/N^3 = 2:1). However, gratifyingly, the selectivity was considerably improved when the reaction was conducted in 2-propanol (IPA) (N^1/N^3 = 9.6:1). Practically, the regioisomer needs not be separated at this stage, and the crude product **14** was subjected to hydrolysis and purified by forming crystalline *N*,*N*-dicyclohexylamine (DCHA) salt. By such a simple procedure, the undesired N^3-regioisomer was removed completely to provide **15** in high yield and high purity (67% based on **12**). Furthermore, the DCHA salt underwent esterification directly with cilexetil chloride to give an ester **16** in high yield (94%). The final intermediate **16** was quite smoothly deprotected by our previously developed debenzylation protocol employing Rosenmund catalyst to furnish Candesartan Cilexetil (**3**) in a high yield (80%).[23]

The quality of **3** obtained was extremely high because the deprotection is carried out under neutral conditions in marked contrast to the previous method (removal of trityl group), which needs strong acid.[20,21]

The present synthesis of **3** is innovative and has the advantages shown below:

1. The biphenyl core is produced by means of C–H arylation and hence has high atom economy[22] and sustainability: atom efficiency[24] of the present process is much higher than previous synthesis using cross coupling reaction (61% versus 34%):
2. The number of steps in the present synthesis is 7, whereas that of the previous one is 10.

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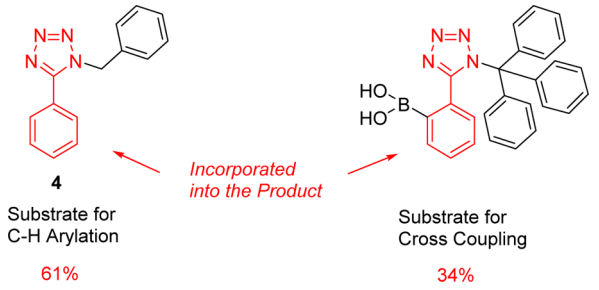

3. The present synthesis is highly convergent using a key common intermediate **12**, from which every ARB is synthesized.
4. It involves easy operation and no need of cryogenic conditions and is able to be conducted under quite mild conditions using very common multipurpose facilities available all over the world.
5. It does not need expensive and/or hazardous reagents.
6. The quality of **3** is extremely high to prove complete equivalence with previous process.
7. Ru and Pd content in the final API produced by the present method were less than the detection limit, which was assayed by IPC analysis. Recovery of Ru catalyst was not tested because of the low price of the catalyst.
8. The process is remarkably practical and thus readily applicable to multihundred kilograms scale commercial production.

In conclusion, sterically demanding TMBSK was found to be extremely efficient as a cocatalyst for the Ru-catalyzed C−H arylation. The catalytic system is economically as well as environmentally sustainable. Versatility and commercial importance of the present process was apparently demonstrated by an application to a novel synthesis of Candesartan Cilexetil. Ready availability and need of very small amount of TMBSK and Ru catalyst as well as ease of operation would form a basic tool in accessing functionalized biaryls of pharmaceutical importance. The use of TMBSK as an additive for C−H activation has never been reported and the insights obtained in the present study would inspire new ideas for C−H activation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental information, including protocols for compound synthesis and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579−2581.
(2) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783−1785.
(3) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826.
(4) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866−4877.
(5) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211−229.
(6) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315−1345.
(7) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879−5918.
(8) Pozgan, F.; Dixneuf, P. H. *Adv. Synth. Catal.* **2009**, *351*, 1737−1743.
(9) Li, B.; Bheeter, C. B.; Darcel, C.; Dixneuf, P. H. *ACS Catal.* **2011**, *1*, 1221−1224.
(10) Arockiam, P. B.; Poirier, V.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 1871−1875.
(11) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 6629−6632.
(12) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332−3335.
(13) Seki, M. *RSC Adv.* **2014**, *4*, 29131−29133.
(14) Ferrer-Flegeau, E.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161−10170.
(15) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858−16860.
(16) Seki, M. *ACS Catal.* **2011**, *1*, 607−610.
(17) Seki, M.; Nagahama, M. *J. Org. Chem.* **2011**, *76*, 10198−10206.
(18) Seki, M. *Synthesis* **2012**, *44*, 3231−3237.
(19) Seki, M. *J. Synth. Org. Chem., Jpn.* **2012**, *70*, 1295−1304.
(20) Kubo, K.; Kohara; Yoshimura, Y.; Inada, Y.; Shibouta, Y.; Furukawa, Y.; Kato, T.; Nishikawa, K.; Naka, T. *J. Med. Chem.* **1993**, *36*, 2343.
(21) Naka, T.; Nishikawa, K.; Kubo, T. Such as 1-(cyclohexyloxycarbonyloxy)ethyl-2-ethoxy-1-((2′-(1H-tetrazol-5-yl)-biphenyl-4-yl)methyl)benzimidazol-7-carboxylate; exhibits antihypertensive activity and strong angiotensin II antagonistic activity. U.S. patent 20020151723, January 16, 2002.
(22) Trost, B. M. *Science* **1991**, *254*, 1471−1477.
(23) Seki, M. *Synthesis*, in press (DOI: 10.1055/s-0034-1378585).
(24) Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273−1283.