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# Highly Efficient Catalytic System for C−H Activation: A Practical Approach to Angiotensin II Receptor Blockers

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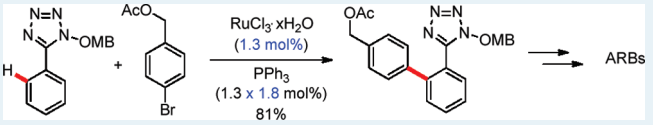
Supporting Information

**ABSTRACT:** An efficient protocol for C−H activation provided a greener and sustainable approach to angiotensin II receptor blockers (ARBs). The use of $PPh_3$ in a specific ratio to inexpensive $RuCl_3 \cdot xH_2O$ resulted in a discovery of an unprecedentedly efficient catalytic system for C−H activation which permitted a practical access to ARBs. The process is atom economical and much greener compared to the previous methods which need stoichiometric amount of hazardous organometallics.




**KEYWORDS:** C−H activation, cross coupling, ruthenium, biaryls, green chemistry

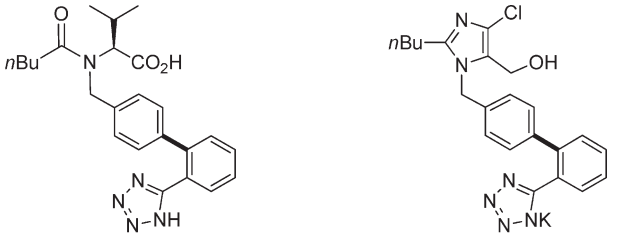
Angiotensin II receptor blockers (ARBs) **1** have aroused keen interest as one of the most efficient antihypertensives because of their high efficacy and safety (Scheme 1).[1−4]

To meet the huge demand for ARBs of more than 1000 t per year used for the clinical treatment worldwide, intensive process research has been conducted to achieve a more efficient and cost-effective synthetic method. ARBs contain a biphenyltetrazole framework as the key and common structural motif. However, the previous synthetic methods have critical drawbacks of the need of stoichiometric amounts of expensive and/or hazardous organometallics such as Grignard reagents and boronic acids to generate the fundamental biphenyltetrazole unit.[1−7] Avoiding potential hazards is a priority in addition to lowering costs in industries.[8,9] To address the challenge, the author has come up with an idea to synthesize them through C−H activation.[10−54] Despite growing amount of information on C−H activation, the commercial application is still challenging. There exist such significant drawbacks such as the need of large amounts of transition metals[10−54] and toxic chemicals like silver salts[32,34,40,53,54] to promote the key aryl−aryl coupling. Described herein is the extremely efficient catalytic system for the C−H activation and application of the technology to a practical synthesis of ARBs **1**.

The strategy for the synthesis of ARBs **1** is outlined in Scheme 2. The C−H bond α to the phenyltetrazole derivative **2** might be activated by means of chelation of Ru with the tetrazole moiety which permits the coupling of **2** with aryl bromide **3**. The resulting biphenyl derivative **4** would readily be converted to bromide **5** which, upon coupling with various functionalized fragments (R-H) followed by deprotection, would furnish ARBs **1** in a highly convergent manner.

The aryl−aryl coupling was first tested by the use of the literature precedent catalyst and procedure.[14] The protected phenyltetrazole **2a**[55,56] was treated with aryl bromide **3** in the presence of $[RuCl_2(benzene)]_2$ (**6a**) (Ru = 10 mol %) and $K_2CO_3$ in NMP at 140 °C to afford the desired biphenyl **4a** in 48% yield (Table 1, Entry 1). However, the price and the catalyst

**Scheme 1. Structures of Compounds 1**




**Scheme 2. Strategy for the Synthesis of ARBs (1)**

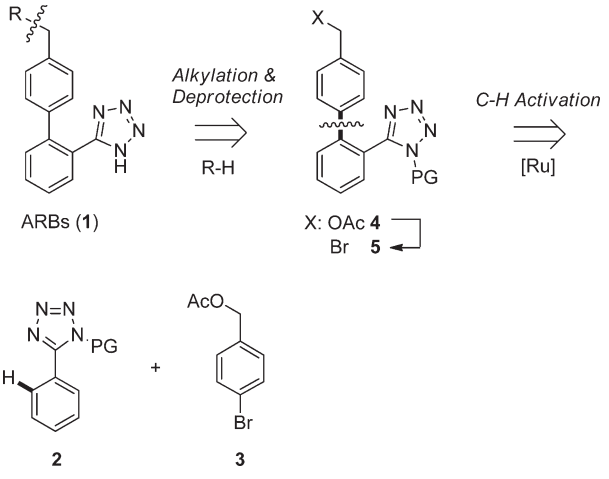



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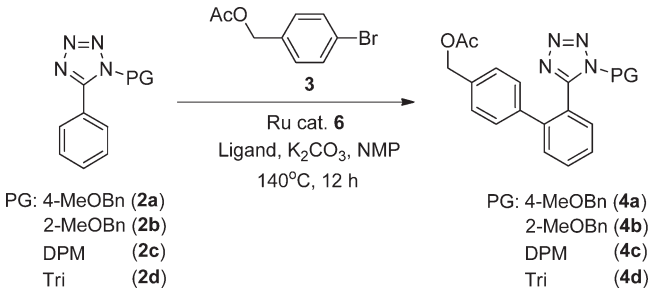
**Table 1. Synthesis of Biphenyltetrazoles 4 through the C−H Activation**




| entry[a] | sub | Ru cat.[b] | ligand | Ru (mol %) | ligand/Ru | yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **2a** | **6a** | $PPh_3$ | 10 | 2.0 | 48[d] |
| 2 | **2a** | **6b** | $PPh_3$ | 10 | 2.0 | 63[d] |
| 3 | **2b** | **6c** | | 10 | 3.0 | 31 |
| 4 | **2b** | **6d** | | 1.3 | 0 | 14 |
| 5 | **2b** | **6d** | $PPh_3$ | 1.3 | 1.0 | 65 |
| 6 | **2b** | **6d** | $PPh_3$ | 1.3 | 1.5 | 70 |
| 7 | **2b** | **6d** | **$PPh_3$** | **1.3** | **1.8** | **81** |
| 8 | **2b** | **6d** | $PPh_3$ | 1.3 | 2.0 | 64 |
| 9 | **2b** | **6d** | $PPh_3$ | 1.3 | 3.0 | 4 |
| 10 | **2b** | **6e** | $PPh_3$ | 1.3 | 1.8 | 3[e] |
| 11 | **2b** | **6e** | $PPh_3$, $H_2O$[f] | 1.3 | 1.8 | 3[e] |
| 12 | **2c**[g] | **6d** | $PPh_3$ | 1.3 | 2.0 | 19,[e] 9 |
| 13 | **2d**[g] | **6a** | $PPh_3$ | 10 | 1.8 | 0 |
| 14 | **2b** | **6d** | $P(2\text{-MePh})_3$ | 1.3 | 1.8 | 0 |
| 15 | **2b** | **6d** | $P(4\text{-MePh})_3$ | 1.3 | 1.8 | 68 |
| 16 | **2b** | **6d** | $P(4\text{-MeOPh})_3$ | 1.3 | 1.8 | 71 |
| 17 | **2b** | **6d** | $P(4\text{-FPh})_3$ | 1.3 | 1.8 | 32 |
| 18 | **2b** | **6d** | $P(4\text{-CF}_3\text{Ph})_3$ | 1.3 | 1.8 | 29 |
| 20 | **2b** | **6d** | $PPh_2Cy$ | 1.3 | 1.8 | 45 |
| 21 | **2b** | **6d** | $PCy_3$ | 1.3 | 1.8 | 17[e] |
| 22 | **2b** | **6d** | XPhos | 1.3 | 1.8 | 7[e] |
| 23 | **2b** | **6d** | dppe | 1.3 | 0.9 | 13[e] |

[a] The biphenylation conditions: **3** (1.1 equiv), $K_2CO_3$ (2 equiv), 140 °C. [b] **6a**: $[RuCl_2(benzene)]_2$, **6b**: $[RuCl_2(COD)]_n$, **6c**: $RuCl_2(PPh_3)_3$, **6d**: $RuCl_3 \cdot xH_2O$, **6e**: $RuCl_3$. [c] Assay yield measured by HPLC. [d] Isolated yield purified by silica-gel column chromatography. [e] Conversion assayed by HPLC. [f] 2.5 equiv relative to **6e** was added. [g] Prepared according to the literature.[62]

loading of **6a** is too high to be applied for commercial production. More affordable $[RuCl_2(COD)]_n$ **6b** resulted in inadequate improvement (63%, Table 1, Entry 2). $RuCl_2(PPh_3)_3$ **6c**, a stable catalyst obtained by the treatment of inexpensive $RuCl_3 \cdot xH_2O$ with excess $PPh_3$[57] was another option for consideration and did give **4b** though in a moderate yield (Table 1, Entry 3). In the meantime, it has been suggested in a recently published literature that unstable catalyst species are expected to provide higher rate acceleration since it would decrease the activation energy by heightening the energy level of the ground state.[58] Taking the concept into consideration, the author hypothesized experiments employing inexpensive $RuCl_3 \cdot xH_2O$ (**6d**) with varying amount of $PPh_3$ might result in a discovery of a better catalytic system (Table 1, Entries 5−9). Gratifyingly, as shown in Table 1 and Figure 1, the highest yield (81%) using an extremely low catalyst loading (1.3 mol %) was

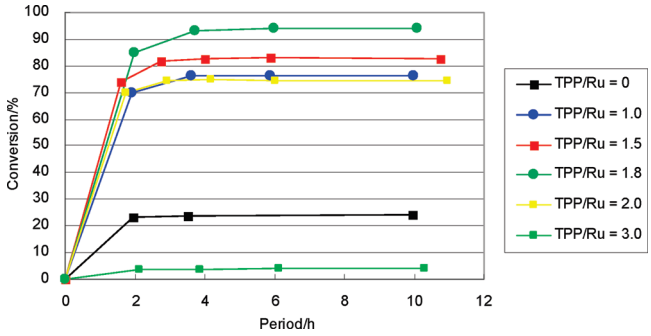
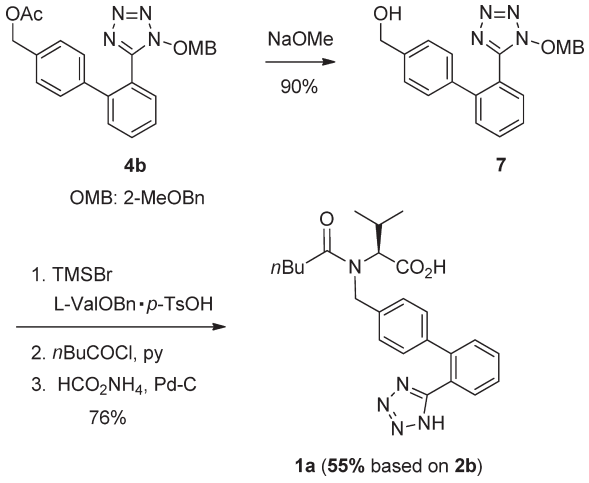



**Figure 1.** Reaction profile of the biphenylation. The biphenylation conditions: see Table 1, Entries 4−9.

**Scheme 3. Synthesis of Valsartan (1a)**




achieved at a specific ratio of $PPh_3$/Ru = 1.8/1 (Table 1, Entry 7). By either lowering or heightening the ratio, the yield remarkably dropped down. The arylation via C−H activation employing inexpensive $RuCl_3 \cdot xH_2O$ (**6d**) has been reported,[15,17] but combination of **6d** with a phosphine ligand has never been demonstrated in this type of reaction.[10−13,59] It is noteworthy that the present reaction did not proceed well in the absence of $PPh_3$ (Table 1, Entry 4). To the best of our knowledge, the catalyst loading (1.3 mol %) achieved in this study represents the lowest value reported so far in this type of the reaction.[10−54,60] The water in $RuCl_3 \cdot xH_2O$ (**6d**) has a significant role for the reaction because neither anhydrous $RuCl_3$ (**6e**) nor **6e** with external addition of equal amount of water to that in **6d** (i.e., 2.5 molar equiv to Ru) catalyzed the reaction (Table 1, Entries 10 and 11).[61] Another substrate **2c** and **2d** carrying a protective group such as sterically more demanding DPM (diphenylmethyl) group and Tri (trityl) group,[5] respectively, were then tested. However, the use of **2c** and **2d** gave either very poor yield or none of the desired product **4c** and **4d** (Table 1, Entries 12 and 13). The benzyl protecting group is thus deduced to be crucial and most appropriate for protecting 5-phenyl-1*H*-tetrazole in the biphenylation reaction.

The effect of the ligand on the reaction was further investigated. As shown in Table 1, Entries 14−16, the steric bulk of the ligand is quite sensitive to the reaction: the use of 2-Me-$Ph_3P$ resulted in no conversion at all while 4-Me-$Ph_3P$ or 4-MeO-$Ph_3P$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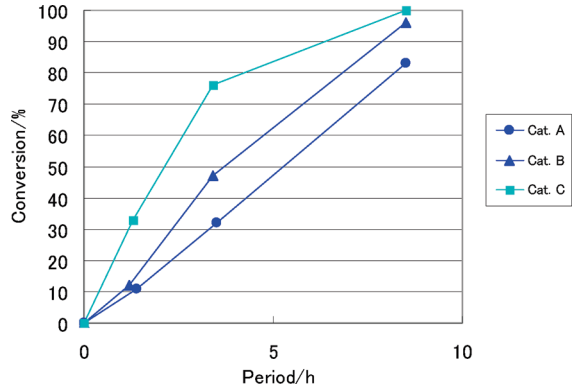


**Figure 2.** Screen of Pd−C for the transfer hydrogenation. Cat A: egg shell, reduced; Cat B: thick shell, oxidized; Cat C: egg shell, oxidized.

gave slightly inferior yields compared to $PPh_3$. Other phosphine ligands carrying an electron-withdrawing group[63] or an alkyl substituent or bidentate phosphine ligands in place of $PPh_3$ resulted in much less activity (Table 1, Entries 17−23). Simple and inexpensive $PPh_3$ is thus the optimal ligand for the biphenylation.

The obtained biphenyl **4b** was readily converted to ARBs **1** as exemplified by the synthesis of Valsartan (**1a**) (Scheme 3). The biphenyl **4b** was first converted to alcohol **7** and in situ brominated and condensed with L-valine benzyl ester. The product was acylated and deprotected by transfer hydrogenation to furnish Valsartan (**1a**) in excellent yield. It should be noticed that proper selection of Pd−C is crucial for the clean deprotection (Figure 2). The oxidized egg shell type Pd−C performed better than thick shell oxidized or egg shell reduced counterparts.[64] The overall yield of **1a** from readily available protected phenyltetrazole (**2b**) is 55% over 5 steps of reaction sequence.

In summary, a quite efficient catalytic system for the C−H activation has been worked out and a practical synthesis of ARBs **1** has been accomplished through the C−H activation. The process is very atom economical: avoiding the use of high molecular weight materials that were not incorporated into the final molecule thus being much shorter, more efficient, and greener compared to the previous methods.[65] The application of the current catalytic system to other substrates to check the scope and limitation and elucidation of the reaction mechanism are under way which will be reported in due course.[66]

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental information. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

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(59) The combination of $RuCl_3 \cdot xH_2O$ with phosphine ligands have been reported in different types of reactions such as a hydroarylation employing ketones as the substrate.[31]
(60) Lower catalyst loadings were reported employing Pd catalyst.[42,50] However, they need expensive phosphine ligands.
(61) Clarification of the role of water in the reaction needs further investigation. It may act as an effective ligand in the transient Ru complex or may facilitate the dissolution of the Ru complex in NMP.
(62) Kumar, K. V.; Dhirenkumar, M.; Sanjay, N., V.; Vijaykumar, D., L., L. (Teva Pharmaceutical Industries Ltd.), Patent WO2008/027385A2 (priority date: August 29, 2006)).
(63) In the case of a hydroarylation employing ketones as the substrate, better results were reported by the use of phosphines bearing an electron-withdrawing group.[31]
(64) The Pd/C catalysts tested in this study have two types of Pd distribution: egg shell and thick shell. In the egg shell type catalyst, Pd distributes close to the surface within 50−150 nm depth. The thick shell type catalyst denotes the one whose Pd distributes until 200−500 nm from the surface.
(65) The use of **2b** as the substrate increases the atom efficiency[8] by 170% compared to the previously employed 5-(2′-boronophenyl)-2-(triphenylmethyl)-2*H*-tetrazole, a well documented substrate for the Suzuki coupling.[5]
(66) The structure of the active complex formed during the reaction is unclear. But, we suppose it has one $PPh_3$ as the ligand, because 0.5 equiv of $PPh_3$ out of initially added 1.8 equiv of $PPh_3$ are required for reduction of $Ru^{III}$ to $Ru^{II}$. The $Ru^{II}/Ru^{IV}$ mechanism involving a ruthenacycle has been well documented in the Ru-catalyzed arylation via C-H activation.[10−13] The addition sequence in the present biphenylation is important as well. Prior heating of $RuCl_3 \cdot xH_2O$ (**6d**) (1.3 mol%) and $PPh_3$ (1.3 × 1.8 mol%) in NMP at 140 °C for 1 h followed by addition of **2b** and **3** (1.1 equiv) and $K_2CO_3$ (2 equiv) at room temperature and then heating the mixture at 140 °C for 12 h resulted in a poor yield of **4b** (42%). It may demonstrate that the transient Ru complex is unstable (active), and, to achieve a higher conversion, the substrates need to coexist with the active catalyst species formed in situ during the reaction.