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Synthesis of Angiotensin II Receptor Blockers by Means of a Catalytic System for C−H Activation

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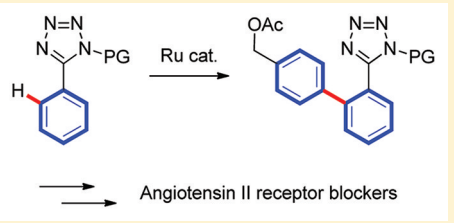
Supporting Information

ABSTRACT: A highly efficient catalytic system for C−H activation has been worked out that involves inexpensive $RuCl_3 \cdot xH_2O$ and a specific amount of PPh_3. This procedure has been successfully applied to a practical synthesis of angiotensin II receptor blockers (ARBs). The residual ruthenium that existed in the reaction mixture was thoroughly removed by treatment with properly selected metal scavengers. The new process permits ready access to the important class of drugs in a highly atom-economical and sustainable manner.



INTRODUCTION

To comply with the recently enhanced need to produce organic substances with minimum amount of reagents and energy, development of a truly efficient synthetic method has recently been a subject of much attention and urgent need. To address the challenge, organic chemists from both academia and industries have focused on a more atom-economical approach whose E-factor is conceptually low.[1] The carbon−carbon bond formation is one of the most important classes of the reactions that enable construction of sophisticated architecture of organic molecules. Especially, the bond formation through the C−H activation[2−4] is one of the most modern and well-recognized tactics of this category.

In the meantime, to produce active pharmaceutical ingredients (APIs) of high quality and lower cost is a significant goal for process chemists in pharmaceutical communities. Through the efforts, the resulting low price APIs can save many lives of people who are otherwise unable to access the drugs that are crucial to maintain their lives. Angiotensin II receptor blockers (ARBs) **1** have received much attention as one of the most efficient antihypertensives due to their high efficacy and safety (Figure 1).[5] Annual production of ARBs is more than 1000 t. ARBs contain a biphenyltetrazole unit as the key and common structural motif. However, the previous synthetic methods have critical drawbacks of need of stoichiometric amounts of expensive and/or hazardous organometallics such as Grignard reagents and boronic acids to install the fundamental biphenyltetrazole framework.[6]

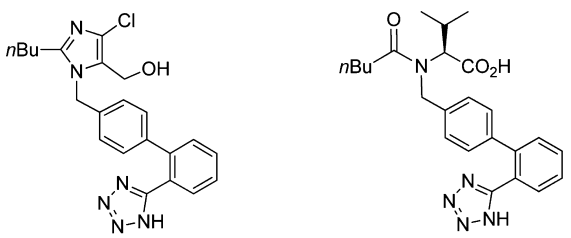


Figure 1. Structure of compounds **1**.

To address the challenge, the authors have considered synthesizing them through C−H activation. New insights into C−H activation have merged on a daily basis. However, the commercial application is still rare and challenging. There are significant drawbacks such as need of unaffordable amount of precious metals and toxic chemicals like silver salts.[4a,c,k,x,y] Described herein is our course of the investigation on an efficient catalytic system for the C−H activation and application of the technology to a practical synthesis of ARBs **1**.[7]

RESULTS AND DISCUSSION

Our strategy for the synthesis of ARBs **1** is shown in Scheme 1. The synthesis utilizes C−H activation for the key biphenyl formation. This type of C−H activation has been demonstrated for benzene derivatives substituted with nitrogen-containing heterocycles such as oxazoline, oxazole, imidazoline, imidazole and pyrazole as the directing group.[2,3a,b,d,g−i,o,q,r] Site-selective C−H activation has been realized through formation of a cyclometalated intermediate by chelation of a transition metal. The C−H bond α to the phenyltetrazole derivative **2** is supposed to be activated as well by means of chelation of Ru with the tetrazole moiety which permits the coupling of **2** with aryl bromide **3a**. The resulting biphenyl derivative **4** might readily be converted to bromide **5** which, upon coupling with various functionalized fragments (R−H) followed by deprotection, would provide ARBs **1** in very short steps and in a highly convergent manner.

Synthesis of 1-*N*-Protected Phenyltetrazole Derivatives. Synthesis of the protected phenyltetrazole **2a** or **7** was

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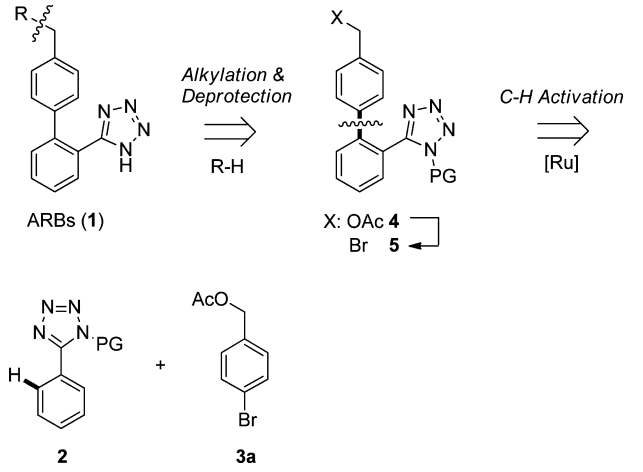
Scheme 1. Strategy for the Synthesis of ARBs (1)

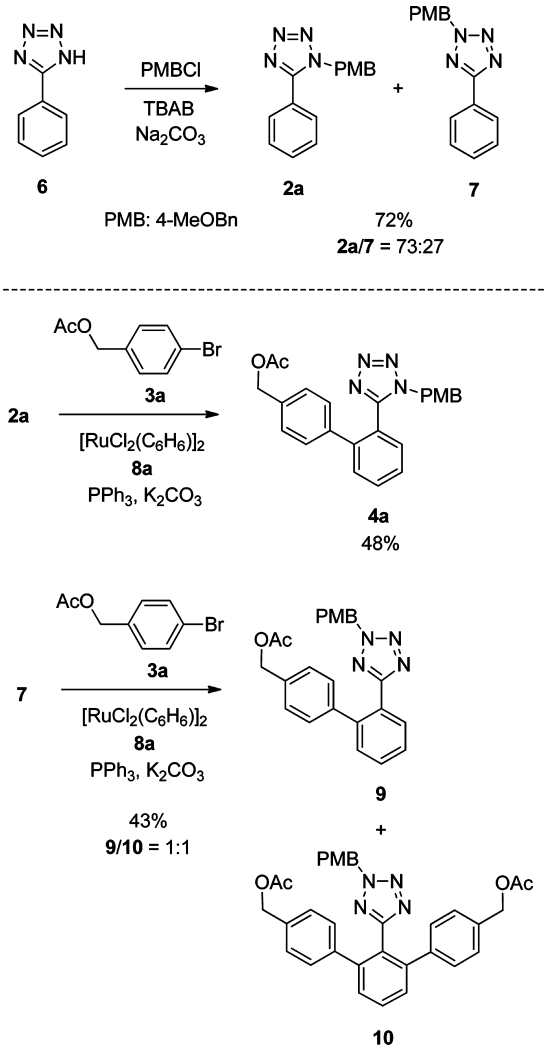


first investigated using 4-methoxybenzyl (PMB) group as the protecting group. In our initial study the compounds were synthesized by alkylation of commercially available 1-phenyl-5*H*-tetrazole **6** (Scheme 2).[6a] However, regioselectivity of the alkylation was poor to give a mixture of 1-*N*- and 2-*N*-protected phenyltetrazoles **2a** and **7** as a mixture of **2a**/**7** = 73:27. In addition, in the biphenylation (*vide infra*), 2-*N*-protected phenyltetrazole **7** provided considerable amount of diarylation byproduct **10** beside the desired monoarylation counterpart **9** even at low conversion of the substrate (Figure 2).[8]

The disappointing results led us to test an alternative approach[9] employing readily available benzylamine derivatives **11a,b** as the starting material and was found to give exclusively the desired 1-*N*-protected phenyltetrazoles **2a,b** in high yields (Scheme 3). 2-MeO-Bn derivative **2b** was stable solids and easy to be isolated by simple crystallization.

Biphenylation through C−H Activation. This type of aryl−aryl coupling in which a nitrogen-containing heterocycle serves as the directing group for the C−H activation has been reported.[2,3a,b,d,g−i,o,q,r] In our initial study, the biphenylation of 1-*N*-protected phenyltetrazole **2** with aryl bromide **3a** was thus examined by the use of the literature precedent catalyst and procedure.[3a] We chose Ru complex as the catalyst. Actually, the Ru catalysis of the direct C−H arylation performs better than the Pd counterpart for the 6-phenylpurine derivatives.[3y,4gg] The protected phenyltetrazole **2a** was treated with aryl bromide **3a** in the presence of $[RuCl_2(C_6H_6)]_2$ (**8a**) (Ru = 10 mol %) and K_2CO_3 in NMP at 140 °C. As expected, the desired biphenyl **4a** was obtained in 48% yield (Table 1, Entry 1). However, the catalyst **8a** is not available on scale and is not applicable to the commercial production. The use of less expensive $[RuCl_2(COD)]_n$ **8b** resulted in unsatisfactory improvement (63%, Table 1, Entry 2). $RuCl_2(PPh_3)_3$ **8c**, obtained as stable catalysts by treatment of inexpensive $RuCl_3 \cdot xH_2O$ with excess PPh_3[10] was tested and found to give **4a** in a moderate yield (Table 1, Entry 3). To address this challenge, the authors focused on a recently published literature. They noted in the literature that unstable catalyst species are expected to provide higher rate acceleration since it would decrease the activation energy by heightening energy level of the ground state.[11] With the concept in mind, the authors came up with an idea in which experiments employing inexpensive $RuCl_3 \cdot xH_2O$ (**8d**) with varying amount of PPh_3 might result in a discovery of a better catalytic system (Table 1, Entries 4−9). As we expected,

Scheme 2. Synthesis of Protected Phenyltetrazoles (2a, 7) and Biphenylation[a]



[a]Biphenylation conditions: for **2a**, **3a** (2.5 equiv), **8a** (Ru = 10 mol %), PPh_3 (20 mol %), K_2CO_3 (4 equiv), 140 °C, 12 h; for **7**, **3a** (1 equiv), **8a** (Ru = 10 mol %), PPh_3 (20 mol %), K_2CO_3 (4 equiv), 140 °C, 12 h.

a dramatical increase of yield (81%) with an extremely low catalyst loading (1.3 mol %) was accomplished by employing a specific amount of PPh_3 (PPh_3/Ru = 1.8/1) (Table 1, Entry 7). By either lowering or heightening the ratio of PPh_3, the conversion remarkably dropped down (Figures 3 and 4). The arylation via C−H activation employing inexpensive $RuCl_3 \cdot xH_2O$ (**8d**) is known,[3c,d] but combined use of **8d** with a phosphine ligand has never been demonstrated in this type of reaction.[2] The present reaction did not take place well in the absence of PPh_3 (Table 1, Entry 4). The reaction with aryl bromides carrying a hydroxyl or an aldehyde group, both of which can provide the intermediate for further elaboration, gave no desired product (Table 1, Entries 10, 11). Those unfavorable results are accounted for by their reducing ability of ruthenium catalysts to undesirable low valent species such as Ru^0 black.[12] There is a possibility that the benzyl cation generated by elimination of the acetoxy group in **3a** can participate in the reaction.[13] However, any products attributable to such transformations were not detected in the reaction mixture. The water in $RuCl_3 \cdot xH_2O$ (**8d**) has a significant role in the reaction because

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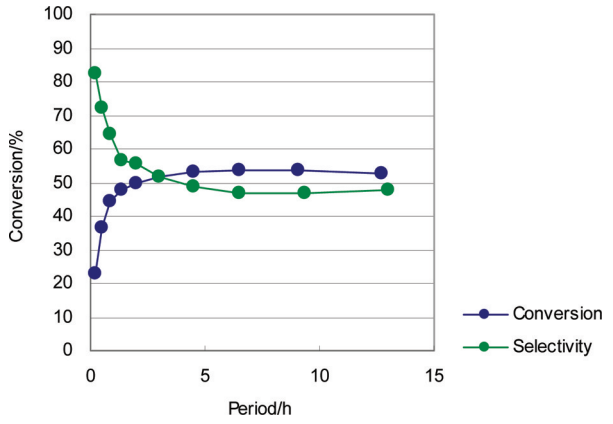
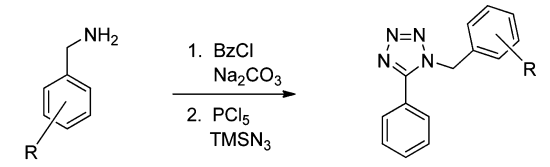


Figure 2. Reaction profile of the biphenylation using 2-PMB-phenyltetrazole **7**. The biphenylation conditions: **3a** (1 equiv), **8a** (Ru = 10 mol %), PPh_3 (20 mol %), K_2CO_3 (4 equiv), 140 °C. Selectivity: **9**/(**9** + **10**) × 100.

Scheme 3. Improved Synthesis of 1-*N*-Protected Phenyltetrazoles 2

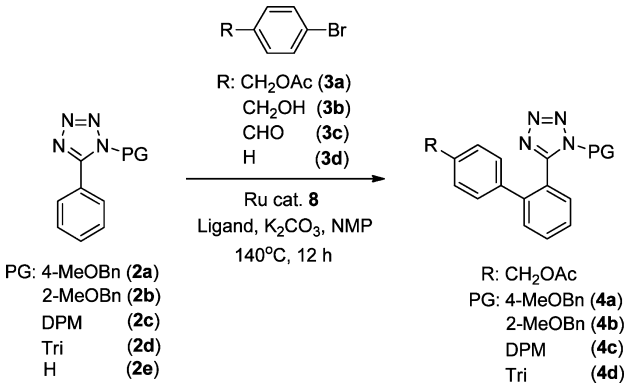


neither anhydrous $RuCl_3$ (**8e**) nor **8e** with external addition of equal amount of water to that in **8d** (i.e., 2.5 molar equiv to Ru) catalyzed the reaction (Table 1, Entries 12 and 13). The role of water in $RuCl_3 \cdot xH_2O$ (**8d**) can be dissolving the catalyst into the reaction mixture. Water itself does not interfere with the reaction, because the biphenylation can be facilitated by employing water as the solvent.[3q] However, in the present case, addition of water more than 5 wt % resulted in a lower conversion, possibly due to the removal of the acetoxy group in bromide **3a** and biphenyl **4**. The resulting benzyl alcohol derivatives are supposed to deteriorate the biphenylation (*vide supra*).

Another substrate **2c** and **2d** carrying a protective group such as sterically more demanding DPM (diphenylmethyl) group and Tri (trityl) group,[6a] respectively, were then tested, because deblocking of the protecting group would be much easier. However, the use of **2c** and **2d** gave either very poor yield or none of the desired product **4c** and **4d**, respectively (Table 1, Entries 14 and 15). In case of **2d**, the trityl group was cleaved under the reaction conditions. Finally, the unprotected 5-phenyl-1*H*-tetrazole **2e** was tested. But no reaction took place possibly due to the catalytic poison caused by the free NH group in **2e**.[6a] From the results descrived above, the methoxy-subsituted benzyl group (PMB, OMB) was chosen as the protecting group for 5-phenyl-1*H*-tetrazole in the biphenylation reaction.

The screening of the phosphine ligands was further conducted. As shown in Table 1, Entries 17–19, 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 though 4-Me-Ph_3P or 4-MeO-Ph_3P gave slightly inferior yields compared to PPh_3. Other phosphine ligands with an electron-withdrawing group or an alkyl substituent or bidentate phosphine ligands instead of

Table 1. Synthesis of Biphenyltetrazoles 4 through C–H Activation



entry[a]	sub.	Ru cat.[b]	ligand	Ru (mol %)	ligand/Ru	yield (%)[c]
1	**2a, 3a**	**8a**	PPh_3	10	2.0	48[d]
2	**2a, 3a**	**8b**	PPh_3	10	2.0	63[d]
3	**2b, 3a**	**8c**		10	3.0	31
4	**2b, 3a**	**8d**		1.3	0	14
5	**2b, 3a**	**8d**	PPh_3	1.3	1.0	65
6	**2b, 3a**	**8d**	PPh_3	1.3	1.5	70
7	**2b, 3a**	**8d**	**PPh_3**	**1.3**	**1.8**	**81**
8	**2b, 3a**	**8d**	PPh_3	1.3	2.0	64
9	**2b, 3a**	**8d**	PPh_3	1.3	3.0	4
10	**2b, 3b**	**8d**	PPh_3	1.3	1.8	0
11	**2b, 3c**	**8d**	PPh_3	1.3	1.8	0
12	**2b, 3a**	**8e**	PPh_3	1.3	1.8	3[e]
13	**2b, 3a**	**8e**	PPh_3, H_2O[f]	1.3	1.8	3[e]
14	**2c**,[g] **3a**	**8d**	PPh_3	1.3	2.0	7
15	**2d**,[g] **3a**	**8a**	PPh_3	10	2.0	0
16	**2e, 3d**	**8a**	PPh_3	10	2.0	0
17	**2b, 3a**	**8d**	$P(2\text{-MePh})_3$	1.3	1.8	0
18	**2b, 3a**	**8d**	$P(4\text{-MePh})_3$	1.3	1.8	68
19	**2b, 3a**	**8d**	$P(4\text{-MeOPh})_3$	1.3	1.8	71
20	**2b, 3a**	**8d**	$P(4\text{-FPh})_3$	1.3	1.8	32
21	**2b, 3a**	**8d**	$P(4\text{-CF}_3\text{Ph})_3$	1.3	1.8	29
22	**2b, 3a**	**8d**	PPh_2Cy	1.3	1.8	45
23	**2b, 3a**	**8d**	PCy_3	1.3	1.8	17[e]
24	**2b, 3a**	**8d**	XPhos	1.3	1.8	7[e]
25	**2b, 3a**	**8d**	dppe	1.3	0.9	13[e]

[a]Biphenylation conditions: **3** (1.1 equiv), K_2CO_3 (2 equiv), 140 °C. [b]**8a**, $[RuCl_2(C_6H_6)]_2$; **8b**, $[RuCl_2(COD)]_n$; **8c**, $RuCl_2(PPh_3)_3$; **8d**, $RuCl_3 \cdot xH_2O$; **8e**, $RuCl_3$. [c]Assay yield of the biphenylation product measured by HPLC. [d]Isolated yield purified by silica-gel column chromatography. [e]Conversion assayed by HPLC. [f]Relative to **8e**, 2.5 equiv was added. [g]Prepared according to a literature.[14]

PPh_3 resulted in much inferior yields (Table 1, Entries 20–25). Fortunately, very simple and inexpensive PPh_3 is thus the optimal phosphine ligand for the biphenylation.

A possible mechanism of the biphenylation is illustrated in Scheme 4. Ru^{II}/Ru^{IV} mechanism is the most well recognized mechanism[2,3t] and the intermediates such as Ru^{II} ruthenacycle derivative **13** has been isolated and demonstrated to provide biphenylation product under biphenylation conditions.[3t,v] From the results shown in Table 1, Entries 4–9, Figures 3 and 4), the use of excess PPh_3 deteriorated the reaction possibly by forming a stable complex like $RuCl_2(PPh_3)_3$ **8c** to kick out the carboxylate anion in **12**[15] which is required for the abstraction of hydrogen atom of the C–H bond. And the excess addition of PPh_3 might effect reduction of the Ru complexes to inactive

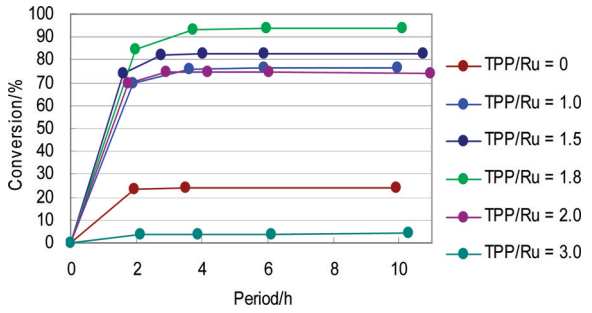


Figure 3. Reaction profile of the biphenylation of **2a** to **4a**. For the biphenylation conditions, see Table 1, Entries 4–9.

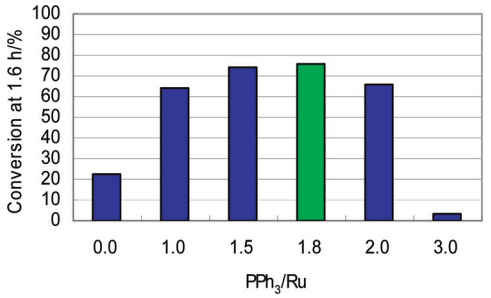
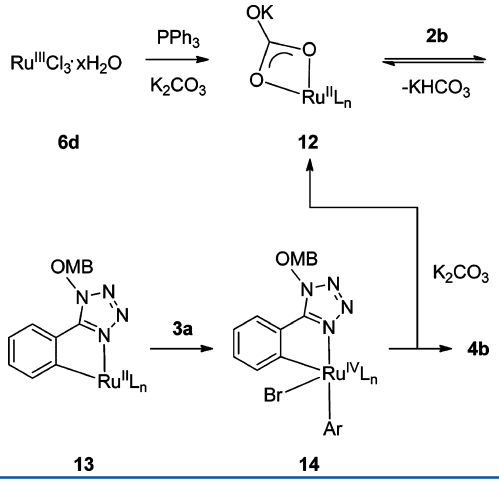


Figure 4. Conversion at 1.4 h in the biphenylation of **2a** to **4a**. For entire reaction profile of the biphenylation, see Figure 3.

Scheme 4. Possible Mechanism of the Biphenylation of 2b to 4b



Ru^0 black to terminate the reaction.[12] Since the use of 1.8 equiv of PPh_3 relative to Ru is optimal and 0.5 equiv of PPh_3 is required for reduction of Ru^{III} to Ru^{II} (Table 1, Entry 7), one molecule of PPh_3 possibly coordinates to Ru as complex **12** in which one L is PPh_3.[16] The addition mode 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 **3a** (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%). As we expected (*vide supra*), 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. Complex **12** reversibly[3t] provides the ruthenacycle **13** which undergoes oxidative addition of aryl bromide **2a** may furnish complex **14**. Complex **14** can be an unstable <16 electron species and thus might rapidly provide the desired biphenyl **4a** and regenerate Ru^{II} complex **12** to complete the catalytic cycle.

Recovery/Removal of the Residual Ru with Metal Scavengers. Drug substances require extremely high quality as governed by good manufacturing practice (GMP).[1] The residual metal, for example, Ru, in active pharmaceutical ingredient (API) must not exceed 10 ppm. To substantiate the absence of the residual metals in API as well as to minimize loss of the precious metals into the waste stream are thus to be indispensable criteria and frequently encountered concern in the process development. With this in mind, we have initiated to explore an efficient and reliable method for recovery of the ruthenium in the biphenylation reaction, a key step of the present synthesis.

The use of metal scavengers for recovery of transition metals has been implemented with some measure of success.[17] They carry functional groups on polymer (e.g., polypropylene, viscose, silica beads) to absorb selectively the precious metals from the mixture (Figure 5). Generally, to achieve an efficient

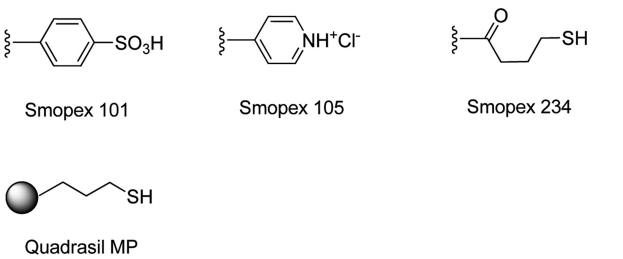


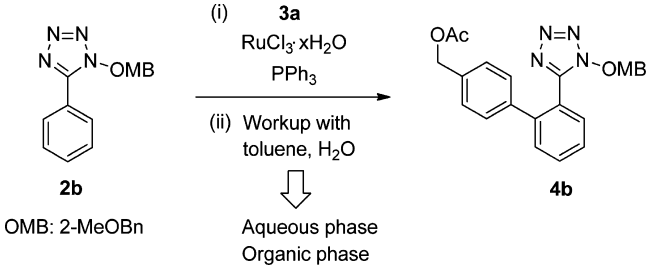
Figure 5. Structure of metal scavengers. "Smopex" is a series of metal scavengers in which functional groups are located on the surface of the fiber. In case of "Quadrasil", the supported materials are slica-gel.

recovery of the metals, proper choice of scavengers carrying specific functional group and other parameters such as solvent, temperature and contact time need to be fully optimized.

The aqueous and organic phases, obtained through the workup after the biphenylation reaction, were submitted to the recovery experiments. By screening a wide range of commercially available scavengers,[18] Smopex-234 and Quadrasil-MP carrying thiol group absorbed Ru in 84.6 and 98.3% yield, respectively (Table 2, Entries 3, 4). In marked contrast, for the aqueous phase, treatment with a combination of Smopex-101 and 234, which have sulfonic acid and thiol group, respectively, recovered Ru more effectively (85.8%) than employing the individual counterpart (64.6 and 35.4%, respectively) (Table 2, Entry 7 versus Entries 5, 6). The difference of the performance of the scavengers may attribute to the different distribution of the metal species among the two phases (oxidized or reduced form with or without ligand). From the results described above, the residual Ru in the biphenylation is able to be removed/recovered effectively by proper use of the metal scavengers.

Conversion to ARBs. The obtained biphenyl **4a,b** was readily converted to ARBs **1** as exemplified by the synthesis of Losartan (**1a**) and Valsartan (**1b**) (Schemes 5–7). The biphenyl **4a** was first converted to alcohol **15** followed by bromination provided bromide **16** which is regarded as a key and common intermediate for ARB synthesis. This compound **16** was coupled with imidazole aldehyde **17** to give the alkylated product **18**

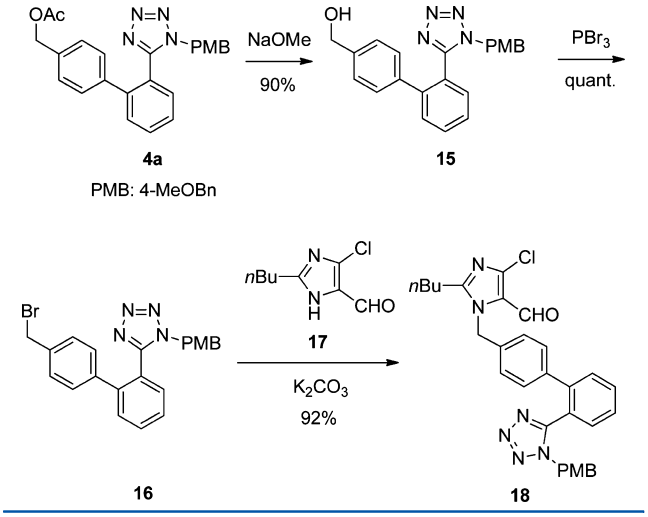
Table 2. Recovery/Removal of the Residual Ru with Metal Scavengers



entry[a]	scavengers	Ru concentration (mg/L)	recovery[b] (%)
Aqueous phase			
	– (Initial)	117	
1	Smopex-101	104	11.1
2	Smopex-105	87	25.6
3	Smopex-234	18	84.6
4	Quadrasil-MP	2	98.3
Organic phase			
	– (Initial)	117	
5	Smopex-101	40	64.6
6	Smopex-234	73	35.4
7	Smopex-101 + 234	16	85.8

[a]Screen was conducted by employing 5 w/v% of the scavenger (0.5 g in 10 mL solution) at 60 °C for 18 h. [b]Assayed by ICP analysis.

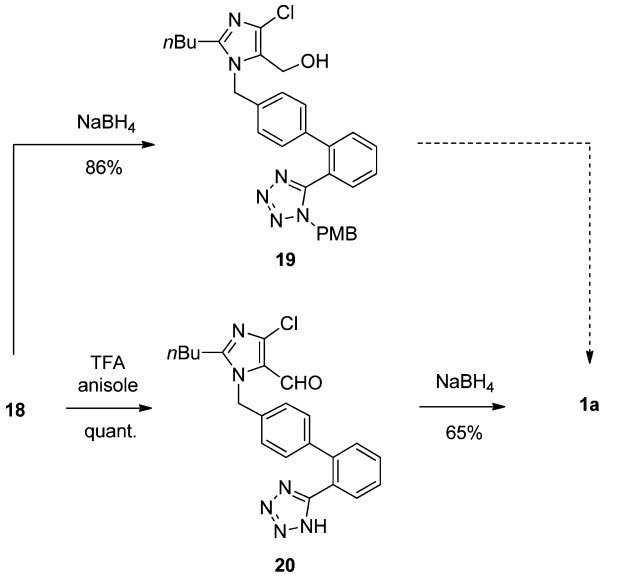
Scheme 5. Synthesis of Losartan Intermediate 18



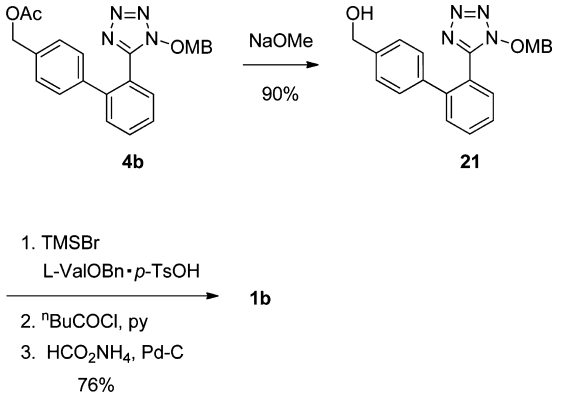
regioselectively[6a] and in high yield (Scheme 4). The removal of the protecting group of the tetrazole unit was conducted before reduction of aldehyde **18** to corresponding alcohol **19** because facile formation of carbocation from benzylic alcohol in **19** would lead to many side products. Treatment of **18** with TFA in the presence of carbocation scavenger (anisole) smoothly removed the *p*-methoxybenzyl (PMB) group to provide the desired deprotected aldehyde **20** quantitatively.[19] The compound **20** was finally converted to Losartan (**1a**) by reduction with $NaBH_4$ in aq. NaOH.

The synthesis of Valsartan (**1b**) started from 2-methoxybenzyl protected biphenyl **4b**, which is derived from readily available 2-methoxybenzyl protected phenyltetrazole **2b**. It was

Scheme 6. Synthesis of Losartan (1a) from 18



Scheme 7. Synthesis of Valsartan (1b)



converted to alcohol **21** and subjected to coupling with L-valine benzyl ester without isolation of potentially hazardous bromide. The *in situ* bromination and subsequent coupling was accomplished by treatment of **21** with TMSBr followed by L-valine benzyl ester in the presence of iPr_2EtN in CH_3CN. The product was acylated and deprotected by transfer hydrogenation to furnish Valsartan (**1b**) in excellent yield. It should be noticed that proper selection of Pd–C is crucial for the clean deprotection. The oxidized egg shell type Pd–C performed better than thick shell oxidized or egg shell reduced counterparts.[20]

CONCLUSIONS

In summary, a highly efficient catalytic system for C–H activation has been developed which was applied to a practical synthesis of ARBs **1**. The efficient catalytic system has been developed by changing the amount of phosphine ligand to Ru. The present work demonstrates importance of this approach to develop an efficient catalytic system. Applying the C–H activation significantly reduces E-value compared to previous methods making the synthesis significantly green. The short steps, easy operation and low cost of the present process would enable a much facile access to ARBs than previous methods.

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EXPERIMENTAL SECTION

General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded with tetramethylsilane used as an internal standard. Silica gel column chromatography was performed using Kieselgel 60 (E. Merck). Thin-layer chromatography (TLC) was carried out on E. Merck 0.25 mm precoated glass-backed plates (60 F_{254}). Development was accomplished using 5% phosphomolybdic acid in ethanol-heat or visualized by UV light where feasible. Ruthenium catalysts **8a**-**8e** were purchased from Johnson Matthey and Sigma Aldrich. Metal scavengers are available at Johnson Matthey. All solvents and reagents were used as received.

1-(p-Methoxybenzyl)-5-phenyl-1H-tetrazole ***2a*** *and 2-(p-Methoxybenzyl)-5-phenyl-1H-tetrazole* ***7***. To a mixture of **6** (14.6 g, 0.1 mol), K_2CO_3 (15.9 g, 0.15 mol), tetra-*n*-butylanmmonium bromide (0.71 g, 2.2 mmol) in water (120 mL) was added dropwise a solution of 4-methoxybenzyl chloride (15.4 g, 98 mmol) in $CHCl_3$ (160 mL) over 1 h at 10 °C and the mixture was stirred at 55 °C for 1 h. The aqueous phase was extracted with $CHCl_3$ and combined organic solution was dried over anhydrous $MgSO_4$ and evaporated. Into the residue in THF (100 mL) were added Ac_2O (6 g, 59 mmol), Et_3N (1.8 g, 18 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.66 g, 5.4 mmol). The mixture was stirred at 20 °C for 1 h. Methanol (20 mL) was added and the mixture was evaporated. The residue was dissolved in AcOEt and washed with water, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatogaraphy (hexane/AcOEt = 3:1) to give **2a**[21] (13.7 g, 52.6%) and **7** (5.1 g, 19.4%). **2a**: mp 37.7−38.3 °C; IR (KBr): ν 1611 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48−7.62 (m, 5H), 7.08−7.13 (m, 2H), 6.84−6.88 (m, 2H), 5.55 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 154.3, 131.1, 129.0, 128.8, 128.6, 125.7, 123.8, 114.4, 55.4, 51.0; MS *m*/*z*: 266 [M]$^+$. **7**: mp 56.5−57.0 °C; IR (KBr): ν 1610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10−8.15 (m, 2H), 7.42−7.51 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.74 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 159.8, 130.1, 129.9, 128.7, 127.3, 126.7, 125.3, 114.2, 56.5, 55.7; EIMS *m*/*z*: 266 [M]$^+$; Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04; Found: C, 67.44; H, 5.13; N, 21.03.

{2′-[2-(p-Methoxybenzyl)-1H-tetrazol-5-yl]biphenyl-4-yl}methyl acetate ***9*** *and {2′-[2-(p-Methoxybenzyl)-2H-tetrazol-5-yl]-1,1′:3′,1″-terphenyl-4,4″-diyl}dimethyl Diacetate* ***10***. A mixture of **7** (228 mg, 0.86 mmol), **3a** (490 mg, 2.1 mmol), $[RuCl_2(benzene)]_2$, **8a** (21.4 mg, 0.086 mmol), PPh_3 (44.9 mg, 0.17 mmol) and K_2CO_3 (474 mg, 3.4 mmol) in NMP (1.7 mL) was stirred at 140 °C. The reaction was monitored by HPLC (Cadenza-CD-C18, 3 μm, 4.6 × 150 mm, CH_3CN/30 mM KH_2PO_4 = 3:2, 225 nm, 40 °C, 1 mL/min) and described in Figure 2. To the mixture was added AcOEt and the mixture was wshed with sat. aq. NaCl dried over anhydrous $MgSO_4$ and evaporated. The authentic samples of **9** and **10** were obtained by purifying the residue by thin layer chromatography (hexane/AcOEt = 1.5:1). **9** (72.9 mg, 21%): oil; IR (KBr): ν 1613, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.84 (m, 1H), 7.52−7.42 (m, 3H), 7.26−7.11 (m, 6H), 6.66−6.80 (m, 2H), 5.56 (s, 1H), 5.10 (s, 1H), 3.81 (s, 3H), 2.12 (s, 3H); ^{13}C-NMR (DMSO-d_6) δ 170.9, 165.4, 159.9, 141.5, 140.9, 134.5, 130.7, 130.4, 130.0, 129.9, 129.4, 127.8, 127.6, 126.2, 125.4, 114.1, 66.1, 56.1, 55.3, 21.1. HRMS: Calcd for $C_{24}H_{22}N_4O_3$, 414.1692; Found 414.1690 [M]$^+$. **10** (106 mg, 22%): mp 103.2−106.4 °C; IR (KBr): ν 1734, 1613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.57 (m, 1H), 7.44−7.40 (m, 2H), 7.10 (s, 8H), 6.98−6.96 (m, 2H), 6.81−6.79 (m, 2H), 5.50 (s, 2H), 5.02 (s, 4H), 3.82 (s, 3H), 2.11 (s, 6H); ^{13}C-NMR (DMSO-d_6) δ 170.9, 163.9, 159.8, 143.2, 140.3, 134.5, 129.9, 129.4, 129.3, 129.2, 127.6, 125.59, 125.55, 114.03, 65.9, 56.0, 55.3, 21.0. HRMS: Calcd for $C_{33}H_{30}N_4O_5$, 562.2216 [M]$^+$; Found 562.2266 [M]$^+$.

1-(p-Methoxybenzyl)-5-phenyl-1H-tetrazole ***2a***. To a mixture of *p*-methoxy benzylamine (181 g, 1.32 mol) and Et_3N (134 g, 1.32 mol) in THF (800 mL) was added dropwise benzoyl chloride (185 g, 1.32 mol) at <16 °C. The mixture was stirred at 20 °C for 3 h and evaporated. To the mixture was added water (400 mL) and the mixture was extracted with AcOEt. The water phase was extracted with AcOEt and combined extracts were washed with sat. aq. NaCl, dried over anhydrous $MgSO_4$ and evaporated. The solids formed were collected by adding AcOEt and dried to give *N*-benzoyl-*p*-methoxybenzylamine (273 g, 85.6%). To a mixture of *N*-benzoyl-*p*-methoxybenzylamine (20 g, 82.9 mmol) in CH_2Cl_2 (161 mL) was added PCl_5 (19.1 g, 91.5 mmol) at −16 to −12 °C over 11 min and the mixture was warmed up to 17 °C for 1 h. The mixture was evaporated to ca. 50 mL under 17 °C. The mixture dissolved in CH_2Cl_2 (112 mL) was added $TMSN_3$ (14.0 g, 122 mmol) at −10 to −8 °C over 12 min. The mixture was stirred at 20 °C for 8 h. Into the mixture was added dropwise sat. aq. $NaHCO_3$ (350 mL). The phase was separated and the aqueous layer was extracted with CH_2Cl_2. The organic phases were combined and washed with sat. aq. $NaCl_2$, dried over anhydrous $MgSO_4$ and evaporated. The crude prodcut was purified by silica gel column chromatography (hexane/AcOEt = 3:1) to give **2a** (22.3 g, 95.8% based on *N*-benzoyl-*p*-methoxybenzylamine) in colorless crystals (content: 94.7% measured by HPLC (Cadenza CD-C18, 4.6 × 150 mm, 3 μm, MeCN/30 mmol/L KH_2PO_4 = 11:9, 225 nm, 40 °C, 1.0 mL/min). The reference sample of **2a** was obtained by recrystallization from AcOEt and hexane), The characterization data of the product **2a** were in good accordance with those obtained by the product from **6** (*vide supra*).

{2′-[1-(p-Methoxybenzyl)-1H-tetrazol-5-yl}biphenyl-4-yl}methyl Acetate ***4a***. A mixture of **2a** (160 mg, 0.60 mmol), **3a** (345 mg, 1.5 mmol), $[RuCl_2(COD)]_n$, **8c** (16.9 mg, 0.06 mmol), PPh_3 (31.8 mg, 0.12 mmol) and K_2CO_3 (333 mg, 2.4 mmol) in NMP (1.2 mL) was stirred at 140 °C for 2 h. Into the mixture was added AcOEt (9 mL) and the mixture was filtered. The filtrate was evaporated to give crude product (504 mg). A portion of the material (419 mg) was purified by silica gel column chromatography (hexane/AcOEt = 4:1) to provide **4a** (131 mg, 63%) in colorless oil. IR (KBr): ν 1612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.68 (m, 1H), 7.57 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.43−7.48 (m, 1H), 7.35 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.24−7.29 (m, 2H), 7.10−7.15 (m, 2H), 6.64−6.72 (m, 4H), 5.08 (s, 2H), 4.75 (s, 2H), 3.73 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.3, 153.9, 140.9, 138.4, 135.6, 131.3, 130.9, 130.0, 129.1, 128.5, 128.2, 127.7, 124.8, 122.5, 113.8, 65.4, 55.1, 50.4, 20.9; EIMS *m*/*z*: 414 [M]$^+$; Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52; Found: C, 69.36; H, 5.15; N, 13.45.

{2′-[1-(p-Methoxybenzyl)-1H-tetrazol-5-yl]biphenyl-4-yl}-methanol ***15***. To a mixture of **4a** (268 mg, 0.65 mmol) in MeOH (15 mL) was added NaOMe in MeOH (125 mg, 0.65 mmol) and the mixture was stirred at 20 °C for 1.5 h. The mixture was evaporated and the residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to provide **15** in cloreless oil (216 mg, 90%). IR (KBr): ν 1612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.67 (m, 1H), 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.41−7.46 (m, 1H), 7.33 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.24−7.29 (m, 2H), 7.08−7.12 (m, 2H), 6.63−6.72 (m, 2H), 4.74 (s, 2H), 4.68 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 154.2, 141.2, 140.8, 137.7, 131.4, 131.0, 130.1, 129.2, 128.5, 127.6, 127.1, 124.9, 122.5, 113.9, 64.4, 55.2, 50.2; EIMS *m*/*z*: 372 [M]$^+$; HRMS: Calcd for $C_{22}H_{20}N_4O_2$, 373.1655 [M + H]$^+$. Found 373.1654 [M + H]$^+$.

5-[4′-(Bromomethyl)biphenyl-2-yl]-1-(p-methoxybenzyl)-1H-tetrazole ***16***. To a solution of **15** (891 mg, 2.39 mmol) in THF (80 mL) was added PBr_3 (1.3 g, 4.8 mmol) at 0 °C over 1.5 h. The mixture was stirred at 20 °C for 4 h. Into the mixture was added water and the mixture was extracted with AcOEt. The organic phase was washed with water, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to afford **16** in yellow oil (1.09 g, quant.). IR (KBr): ν 1611 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.68 (m, 1H), 7.55−7.59 (m, 1H), 7.44−7.49 (m, 1H), 7.34−7.38 (m, 1H), 7.28−7.33 (m, 2H), 7.07−7.13 (m, 2H), 6.64−6.73 (m, 4H), 4.75 (s, 2H), 4.46 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 154.0, 140.8, 138.7, 137.5, 131.5, 131.1, 130.1, 129.4, 129.3, 128.9, 127.9, 124,9, 122.7, 114.0, 55.3, 50.6, 32.7; EIMS *m*/*z*: 434 [M]$^+$; HRMS: Calcd for $C_{22}H_{20}N_4OBr$, 435.0820 [M + H]$^+$. Found 435.0821 [M + H]$^+$.

1-(o-Methoxybenzyl)-5-phenyl-1H-tetrazole ***2b***. To a mixture of *o*-methoxy benzylamine (300 g, 2.19 mol) and Na_2CO_3 (232 g, 2.19

mol) in a mixture of water (1500 mL) and toluene (1500 mL) was added dropwise benzoyl chloride (307 g, 2.19 mol) at 3−8 °C. The mixture was stirred at 20 °C for 20 min and evaporated. The solids formed was dissolved by adding CH_2Cl_2 and water. The organic phase was separated and washed with water, dried over anhydrous $MgSO_4$ and evaporated. The solids formed were collected by adding isopropyl ether and dried to give *N*-benzoyl-*o*-methoxybenzylamine (530 g, quant.). To a mixture of *N*-benzoyl-*o*-methoxybenzylamine (16 g, 66.3 mmol) in CH_2Cl_2 (139 mL) was added PCl_5 (15.2 g, 73.1 mmol) at −15 to −11 °C over 11 min and the mixture was warmed up to 21 °C for 2 h. The mixture was evaporated under 20 °C. To the residue dissolved in CH_2Cl_2 (111 mL) was added $TMSN_3$ (11.2 g, 97.5 mmol). The mixture was stirred at 20 °C for 4 h. Into the mixture was added dropwise sat. aq. $NaHCO_3$ (280 mL). The phase was separated and the aqueous layer was extracted with CH_2Cl_2. The organic phases were combined and washed with sat. aq. $NaCl_2$, dried over anhydrous $MgSO_4$ and evaporated. The solids formed were collected by adding AcOEt to provide **2b** (16.7 g, 94%) in colorless crystals. mp 100−102 °C; IR (KBr): ν 1603 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.76 (dd, J = 7.9, 2.2 Hz, 2H), 7.65−7.60 (m, 3H), 7.32 (td, J = 8.0, 1.5 Hz, 1H), 7.09 (dd, J = 8.0, 1.5 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.92 (t, J = 8.0 Hz, 1H), 5.64 (s, 2H), 3.58 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 156.6, 154.3, 131.0, 130.1, 129.5, 129.0, 128.7, 124.0, 122.2, 120.4, 111.0, 55.2, 46.9. SIMS m/z: 267 $[M + H]^+$; Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04; Found: C, 67.47; H, 5.12; N, 20.92.

{2′-[1-(o-Methoxybenzyl)-1H-tetrazol-5-yl]biphenyl-4-yl}methyl Acetate ***4b***. A mixture of $RuCl_3{\cdot}xH_2O$ (**8d**) (Ru 40.01%, 5.7 mg, 23 μmol), PPh_3 (10.4 mg, 40.3 μmol), **2b** (481 mg, 1.81 mmol), K_2CO_3 (499 mg, 3.61 mmol), **3a** (455 mg, 1.99 mmol) and NMP (1.9 mL) was stirred under N_2 atmosphere at 140 °C for 12 h. The mixture was cooled to 20 °C and it was diluted with AcOEt (10 mL) and washed twice with water, dried over anhydrous $MgSO_4$ and evaporated. The residue contained **4b** (607 mg, 81%) as assayed by HPLC (Cadenza CD-C18, 3 μm, 4.6 × 150 mm, CH_3CN/30 mM KH_2PO_4 (3:2), 225 nm, 40 °C). The authentic sample of **4b** was obtained by purification with silica-gel column chromatography using a mixture of hexane/AcOEt = 4:1). mp 117−118 °C; IR (KBr): ν 1735, 1603 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.65−7.62 (m, 1H), 7.57−7.56 (m, 1H), 7.45−7.43 (m, 2H), 7.27−7.14 (m, 5H), 6.80−6.70 (m, 3H), 5.09 (s, 2H), 4.76 (s, 2H), 3.51 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 170.2, 156.6, 154.1, 141.1, 138.4, 135.7, 131.5, 130.9, 130.3, 130.2, 130.1, 128.5, 128.0, 127.8, 122.5, 121.3, 120.2, 110.9, 64.9 55.1, 45.9, 20.6; MS: m/z = 415 $[M + H]^+$; Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52; Found: C, 69.55; H, 5.11; N, 13.45.

{2′-[1-(o-Methoxybenzyl)-1H-tetrazol-5-yl]biphenyl-4-yl}-methanol ***21***. To a solution of **4b** (1.01 g, 2.44 mmol) in MeOH (5.0 mL), was added MeONa in MeOH (28 wt %) (24 μL, 23 mg, 0.12 mmol) and the mixture was stirred for 9 h. The mixture was evaporated and the residue was dissolved in $CHCl_3$ and washed, dried over $MgSO_4$ and evaporated. The solids formed were collected by adding hexane to provide **21** (820 mg, 90%) in colorless crystals. mp 139−141 °C; IR (KBr): ν 3398, 1605 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.73 (td, J = 7.8, 2.3 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.59−7.55 (m, 2H), 7.26 (td, J = 7.9, 1.6 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 8.2 Hz, 2H), 6.91 (dd, J = 7.9, 1.6 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 6.81 (t, J = 7.9 Hz, 1H), 5.22 (t, J = 5.9 Hz, 1H), 4.93 (s, 2H), 4.49 (d, J = 5.9 Hz, 2H), 3.50 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 156.6, 154.2, 142.1, 141.4, 137.1, 131.4, 131.1, 130.8, 130.2, 128.1, 127.8, 127.5, 126.5, 122.5, 121.3, 120.2, 110.9, 62.4, 55.1, 45.8; MS: m/z = 373 $[M + H]^+$; Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.41; N, 15.04; Found: C, 70.76; H, 5.27; N, 15.01.

1-Diphenylmethyl-5-phenyl-1H-tetrazole ***2c***. A mixture of 5-phenyl-1*H*- tetrazole (14.6 g, 0.1 mol), Na_2CO_3, nBu$_4$NBr (710 mg, 2.2 mmol) and benzhydryl chloride (19.9 g, 98 mmol) in a mixture of $CHCl_3$ (160 mL) and water (120 mL) was stirred at 2 °C for 3 h and at 20 °C for 3 h and finally at 55 °C for 3 h. The organic phase was separated and washed with water, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (hexane/ACOEt = 4:1) to provide **2c** in colorless crystals (13.5 g, 43%). mp 170.4−171.6 °C; IR (KBr): ν 1601 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.57−7.38 (m, 5H), 7.367−7.365 (m, 6H), 7.26−7.21 (m, 4H), 6.78 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ 155.0, 137.5, 131.4, 129.3, 129.1, 129.0, 128.8, 128.2, 123.9, 65.9. Anal. Calcd for $C_{20}H_{16}N_4$: C, 76.90; H, 5.16; N, 17.94; Found: C, 76.70; H, 4.97; N, 17.92.

{2′-[1-(Diphenylmethyl)-1H-tetrazol-5-yl]biphenyl-4-yl}methyl Acetate ***4c***. A mixture of $RuCl_3{\cdot}xH_2O$ (**8d**) (Ru 40.01%, 6.7 mg, 27 μmol), PPh_3 (12.2 mg, 46.5 μmol), **2c** (552 mg, 1.77 mmol), K_2CO_3 (488 mg, 3.53 mmol), **3a** (445 mg, 1.94 mmol) and NMP (2.2 mL) was stirred under N_2 atmosphere at 140 °C for 12 h. The mixture was cooled to 20 °C and it was diluted with AcOEt (10 mL) and washed twice with water, dried over $MgSO_4$ and evaporated. The residue wqas purified by preparative TLC (hexane/AcOEt = 4:1) to afford **4c** (9.5 mg, 7%) in colorless crystals. mp 140.9−141.2 °C; IR (KBr): ν 1735, 1600 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.66−7.64 (m, 1H), 7.58−7.56 (m, 1H), 7.46−7.43 (m, 1H), 7.29−7.27 (m, 1H), 7.24−7.21 (m, 2H), 7.19−7.16 (m, 8H), 6.69 (brs, 1H), 6.10 (s, 1H), 5.04 (s, 1H), 2.14 (s, 3H); ^{13}C-NMR (DMSO-d_6) δ 170.8, 155.1, 141.4, 138.5, 136.7, 135.9, 131.6, 131.3, 130.4, 129.2, 128.6, 128.5, 128.3, 128.0, 127.9, 122.8, 65.9, 65.4, 21.0. HRMS: Calcd for $C_{29}H_{24}N_4O_2$, 460.1899 $[M]^+$; Found 460.1897 $[M]^+$.

Recovery of Ru from the Mixure Obtained through the Bipnenylation of ***2b*** *to* ***4b***. A mixture of $RuCl_3{\cdot}xH_2O$ (**8d**) (Ru 40.01%, 501 mg, 1.98 mol), PPh_3 (1.04 mg, 3.96 mmol), **2b** (42.2 g, 159 mmol), K_2CO_3 (43.8 g, 317 mmol), **3a** (39.9 g, 174 mmol) and NMP (169 mL) was stirred under N_2 atmosphere at 140 °C for 12 h. The conversion of this reaction was 74%. The mixture was cooled to 20 °C, and toluene (900 mL) and water (480 mL) were added. The obtained organic and water phases (combined volume was 1.6 L) were separated and allowed to test removal of Ru with metal scavengers. The content of Ru in both phases was assayed by ICP analysis and deduced to be 130 mg/L. A part of the sample solution was mixed with 5 mol % of the metal scavengers tested at inidicated temperature and for appropiate period (Table 2). Then, after filtration of the mixture, the concentartion of Ru in the filtrate was assayed by ICP analysis, which is shown in Table 2.

2-Butyl-4-chloro-1-({2′-[1-(p-methoxybenzyl)-1H-tetrazol-5-yl]-biphenyl-4-yl}-methyl)imidazole-5-carbaldehyde ***18***. A mixture of **16** (93 mg, 0.213 mmol), **17** (40.5 mg, 0.217 mmol) and K_2CO_3 (30.3 mg, 0.219 mmol) in *N*,*N*-dimethyl acetamide (1 mL) was stirred at −10 °C for 4 h followed by at rt for 4 h. The mixture was filtered and solids were washed with AcOEt. The combined AcOEt solution was evaporated. The residue was purified by slica-gel column chromatography (AcOEt/hexanes = 1:2) to afford **18** (0.106 g, 92%) in colorless crystals. mp 47.1−48.6 °C; IR (KBr): ν 1664 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.75 (s, 1H), 7.65 (t, J = 7.6, 1H), 7.53 (d, J = 7.6, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.70 (q, J = 8.8 Hz, 4H), 5.52 (s, 2H), 4.74 (s, 2H), 3.72 (s, 3H), 2.61 (t, J = 7.6 Hz, 2H), 1.61−1.73 (m, 2H), 1.30−1.42 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 177.6, 159.5, 154.3, 153.9, 143.0, 140.7, 138.5, 135.4, 131.4, 131.1, 130.1, 129.3, 129.1, 127.9, 126.7, 124.9, 124.1, 122.6, 114.0, 55.3, 50.5, 47.9, 29.3, 26.6, 22.5, 13.8; EIMS (m/z): 540 $[M]^+$; HRMS: Calcd for $C_{30}H_{30}N_6O_2Cl$, 541.2119 $[M + H]^+$. Found 541.2111 $[M + H]^+$.

2-Butyl-4-chloro-1-({2′-[1-(p-methoxybenzyl)-1H-tetrazol-5-yl]-biphenyl-4-yl}-methyl)imidazole-5-methanol ***19***. To a solution of **18** (438 mg, 0.8 mmol) in MeOH (0.5 mL) was added $NaBH_4$ (90.8 mg, 2.4 mmol) at −10 °C and the mixture was stirred at 20 °C for 1.5 h. Then, $NaBH_4$ (30.3 mg, 0.8 mmol) was added and the mixture was stirred at 30 °C for 1 h. 50% aq. AcOH (0.029 mL) was added and the mixture was stirred at 20 °C for 30 min. Water (1.6 mL) was added and the mixture was stirred at 20 °C for 2 h and at 5−10 °C for 30 min. The solids formed were collected to afford **19** (373 mg, 86%) in colorless crystals. mp 119.5−120.8 °C; IR (KBr): ν 1612, 1583 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.62−7.68 (m, 1H), 7.51−7.55 (m, 1H), 7.42−7.50 (m, 1H), 7.30−7.35 (m, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 6.64−6.75 (m, 4H), 5.18 (s, 2H), 4.78 (s, 2H) 4.49 (d, J = 6.4 Hz, 2H), 3.73 (s, 3H), 2.54 (dd, J = 7.6 Hz, 2H), 1.60−1.70 (m, 2H), 1.28−1.41 (m, 2H), 0.88 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.5, 153.9, 148.4, 140.9, 138.4, 135.9, 131.4, 131.0, 130.1, 129.3, 129.1, 127.9, 127.5, 126.3, 124.9, 124.6, 122.6, 114.0, 55.3, 53.2,

50.6, 47.2, 29.8, 26.9, 22.5, 13.9; HRMS: Calcd for $C_{30}H_{32}N_6O_2Cl$, 543.2275 $[M + H]^+$; Found 543.2271 $[M + H]^+$.

2-Butyl-4-chloro-1-{[2′-(1H-tetrazol-5-yl)biphenyl-4-yl}methyl)-imidazole-5-carbaldehyde **20**.[5a] A mixture of **18** (93 mg, 0.172 mmol), anisol (63 mg, 0.59 mmol) and TFA (1.3 mL) was stirred at 20 °C for 3 h, at 45 °C for 1 h, 65 °C for 4 h and finally at 80 °C for 5 h. The mixture was evaporated and the residue was treated with 1 N aq. KOH (5 mL), water (20 mL) and toluene (20 mL). The aqueous phase was washed with toluene and acidified (pH 1.8) by adding 1 N HCl. The product was extracted by AcOEt and the organic solution was washed with sat. aq. NaCl, dried over anhydrous MgSO4 and evaporated to afford **20** (89.4 mg, quant.) in amorphous solid. IR (KBr): ν 1667, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 8.04 (dd, J = 7.7, 1.5 Hz, 1H), 7.60 (td, J = 7.7, 1.5 Hz, 1H), 7.54 (td, J = 7.7, 1.5 Hz, 1H), 7.42 (dd, J = 7.7, 1.5 Hz, 1H), 7.18 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.2 Hz, 2H), 5.54 (s, 2H), 2.64 (t, J = 7.7 Hz, 2H), 1.68 (quint, J = 7.7 Hz, 2H), 1.36 (sext, J = 7.7 Hz, 2H), 0.89 (t, J = 7.7 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 177.4, 173.3, 153.9, 140.6, 140.4, 138.1, 135.0, 130.6, 130.1, 128.7, 127.4, 125.4, 123.5, 46.6, 28.0, 24.9, 21.1, 13.0; SIMS m/z: 421 $[M + H]^+$; HRMS: Calcd for $C_{22}H_{21}N_6OCl$, 421.1544 $[M + H]^+$; Found 421.1541 $[M + H]^+$.

2-Butyl-4-chloro-1-{[2′-(1H-tetrazol-5-yl)biphenyl-4-yl}methyl)-imidazole-5-methanol (Losartan) **1a**.[6a] To a mixture of **20** (101 mg, 0.24 mmol), 1N aq. NaOH (0.24 mL) and water (0.24 mL), $NaBH_4$ (18.4 mg, 0.486 mmol) was added at 5 °C. The mixture was stirred at 5 °C for 25 min and at 20 °C for 3 h. Into the mixture was added $NaBH_4$ (8.6 mg, 0.23 mmol) at 20 °C and the mixture was stirred at the same temperature for 1 h. Into the mixture was added water (0.5 mL) and the mixture was washed with diisopropyl ether. The mixture was acidified (pH 2) by adding 1% HCl and extracted with AcOEt. The organic phase was separated and washed with sat. aq. NaCl, dried over anhydrous $MgSO_4$ and evaporated to provide **1a** (66.1 mg, 65%). The pure sample of **1a** was obtained by recrystallization from a mixture of CH_3CN and water (3:4). mp 161−164 °C; IR (KBr): ν 3374, 1604, 1579, 1469 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.68 (t, J = 7.4 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H,), 7.08 (d, J = 8.2 Hz, 2H), 7.02 (d, J = 8.2 Hz, 2H), 5.23, (s, 1H), 4.32 (s, 1H), 2.45 (t, J = 7.5 Hz, 2H), 1.44 (quint, J = 7.5 Hz, 2H), 1.23 (sext, J = 7.5 Hz, 2H), 0.80 (t, J = 7.7 Hz, 3H); SIMS:m/z 423 $[M + H]^+$; HRMS: Calcd for $C_{22}H_{24}N_6OCl$, 423.1700 $[M + H]^+$; Found 423.1696 $[M + H]^+$.

N-Pentanoyl-N-{[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-L-valine (Valsartan) **1b**. A mixture of **21** (1.00 g, 2.69 mmol) and TMSBr (0.711 mL, 822 mg, 5.37 mmol) in CH_3CN (5.0 mL) was stirred at 50 °C for 4.5 h. The mixture was cooled to 20 °C and to the mixture were added iPr$_2$EtN (1.57 g, 12.1 mmol) and L-valine benzyl ester p-toluenesulfonate (1.53 g, 4.03 mmol) and CH_3CN (4.0 mL). The mixture was stirred at 50 °C for 2 h. After cooling the mixture to 20 °C, it was diluted with AcOEt (20 mL) and water (1.7 mL). The aqueous phase was extracted with AcOEt and combined organic phases were washed with sat. aq. NaCl, dried over $MgSO_4$ and evaporated. The residue was dissolved in $CHCl_3$ and 84.1% portion of this material was evaporated. Into the residue were added toluene (6.4 mL), pyridine (0.275 mL, 0.269 g, 3.40 mmol) and n-pentanoyl chloride (0.376 mL, 0.382 g, 3.17 mmol) and the mixture was stirred at 20 °C for 4 h and at 40 °C for 2 h. Pyridine (92.8 mg, 1.17 mmol) and nBuCOCl (141 mg, 1.17 mol) were added and it was stirred at 40 °C for 3 h. The mixture was cooled down to 20 °C and 1 M HCl (5 mL) and AcOEt (20 mL) were added. The aqueous phase was extracted with AcOEt and the combined extracts were washed successively with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over $MgSO_4$ and evaporated. The residue was purified by silica-gel column chromatography using a mixture of toluene/AcOEt = 50:1 to 5:1 to afford n-pentanoyl derivative (1.47 g). It was dissolved in 2-propanol (4.53 g). To a portion (800 mg) of the solution were added Pd/C (5%Pd, water: 58.8 wt %, 128 mg), ammonium formate (96.2 mg, 1.53 mmol) and water (0.51 mL) and the mixture was stirred at 20 °C for 14 min and at 45 °C for 6 h. The mixture was filtered by adding 2-propanol (10 mL). The filtered solids were washed with 2-propanol (5 mL) and the combined solution was evaporated. Into the residue were added 0.5 M NaOH (2.0 mL), water (7 mL) and TBME (5 mL). The aqueous phase was washed with TBME and treated with 1N HCl (1.7 mL) and AcOEt (40 mL). The aqueous phase was extracted twice with AcOEt and the combined extracts were washed with sat. aq. NaCl, dried over $MgSO_4$ and evaporated. The solids formed were collected by adding a mixture of cyclohexane and AcOEt to afford **1b** (99.5 mg, 76%) in colorless crystals. mp 70−95 °C (Valsartan **1b** is known to exist in several crystalline forms (P. Bühimayer, F. Ostermayer, T. Schmidlin (Ciba-Geigy), EP0443983A1 (priority date: February 19, 1990)). Control of the polymorph was not examined in this study. IR (KBr): ν 1730, 1619 cm^{-1}; ^1H NMR (DMSO-d_6): (C_M: major rotamer; C_m: minor rotamer): δ 16.3 (brs, 1H), 12.6 (brs, 1H), 7.70−7.63 (m, 2H, C_M, C_m), 7.58−7.53 (m, 2H, C_M, C_m), 7.20 (d, J = 8.2 Hz, 1H, C_M), 7.08 (d, J = 8.2 Hz, 1H, C_m), 7.07 (d, J = 8.2 Hz, 1H, C_M), 6.97 (d, J = 8.2 Hz, 1H, C_m), 4.62 (s, 2H, C_M), 4.48 (d, J = 15.2 Hz, 1H, C_m), 4.46 (d, J = 10.3 Hz, 1H, C_M), 4.43 (d, J = 15.2 Hz, 1H, C_m), 4.08 (d, J = 10.5 Hz, 1H, C_m), 2.53−2.45 (m, 2H, C_m), 2.22−2.12 (m, 1H, C_M, C_m), 2.21 (dt, J = 15.8, 7.9 Hz, 1H, C_M), 2.03 (dt, J = 15.8, 7.9 Hz, 1H, C_M), 1.54 (quint, J = 6.9 Hz, 2H, C_m), 1.41 (dquint, J = 14.1, 7.9 Hz, 1H, C_M), 1.37 (dquint, J = 14.1, 7.9 Hz, 1H, C_M), 1.31 (sext, J = 6.9 Hz, 2H, C_m), 1.15 (sext, J = 7.9 Hz, 2H, C_M), 0.93 (d, J = 6.9 Hz, 3H, C_m), 0.93 (d, J = 7.9 Hz, 3H, C_M), 0.88 (t, J = 6.9 Hz, 3H, C_m), 0.76 (t, J = 7.9 Hz, 3H, C_M), 0.75 (d, J = 7.9 Hz, 3H, C_M), 0.70 (d, J = 6.9 Hz, 3H, C_m); HRMS: Calcd for $C_{24}H_{29}N_5O_3$, 435.2270 $[M]^+$; Found 435.2267 $[M]^+$.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H- and ^{13}C NMR spectra for unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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