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A Convergent Approach to the Total Synthesis of Telmisartan via a Suzuki Cross-Coupling Reaction between Two Functionalized Benzimidazoles

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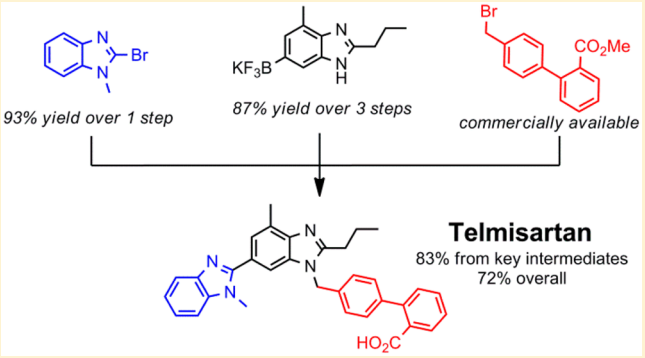
Supporting Information

ABSTRACT: A direct and efficient total synthesis has been developed for telmisartan, a widely prescribed treatment for hypertension. This approach brings together two functionalized benzimidazoles using a high-yielding Suzuki reaction that can be catalyzed by either a homogeneous palladium source or graphene-supported palladium nanoparticles. The ability to perform the cross-coupling reaction was facilitated by the regio-controlled preparation of the 2-bromo-1-methylbenzimidazole precursor. This convergent approach provides telmisartan in an overall yield of 72% while circumventing many issues associated with previously reported processes.

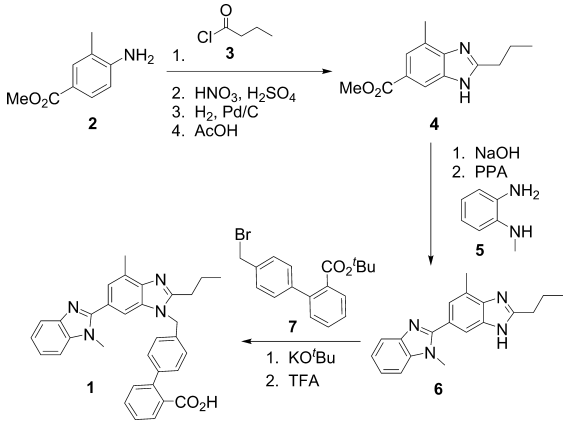


Telmisartan (**1**) is a potent angiotensin II receptor antagonist used in the treatment of essential hypertension.[1−3] It is one of the most efficacious drugs in its class, boasting the longest half-life, a high protein binding affinity, and a low daily dosage.[4,5] The drug is currently marketed under the brand name of Micardis and provides additional benefits against vascular and renal damage caused by diabetes and cardiovascular disease.[6−8]

Previously reported syntheses of telmisartan, including the commercial process, invariably rely on the sequential formation of the two benzimidazole moieties through cyclization of appropriately substituted aniline precursors. The high temperatures and extreme pH conditions required by this strategy result in lower yields and significant byproduct formation. Given the recent loss of telmisartan patent protection in the US, taking a fresh look at the construction of this widely prescribed drug is a timely and relevant endeavor. We now report a fundamentally different approach based on a Pd-catalyzed coupling of two structurally distinct benzimidazole units. Our synthetic scheme is more convergent and higher yielding than recently reported efforts, reaching telmisartan in an overall yield of 72% in comparison to the previously reported highest yield of 50%.[9]

The original synthesis of telmisartan was developed by Ries et al. in 1993[10] (Scheme 1), beginning with the stepwise construction of the central benzimidazole ring from 4-amino-3-methylbenzoic acid methyl ester (**2**). Saponification of the resulting substituted benzimidazole **4** was followed by condensation with *N*-methyl-1,2-phenylenediamine (**5**) using polyphosphoric acid at elevated temperature (150 °C) to afford the functionalized dibenzimidazole **6**. Alkylation of the latter with 4′-(bromomethyl)-2-biphenylcarboxylic acid *tert*-butyl ester (**7**) followed by hydrolysis of the resulting ester provided telmisartan in 21% overall yield over eight linear steps.

Scheme 1. Original Synthesis of Telmisartan



The elevated temperature and acidic conditions required during the second cyclization step adversely impact both product yield and purity, a major drawback of this original route that has not been addressed in subsequent process improvements to this basic method.[9,11−13] In a recent report, the cyclocondensation of an aromatic aldehyde with *o*-phenylenediamine was explored as an alternative path to the

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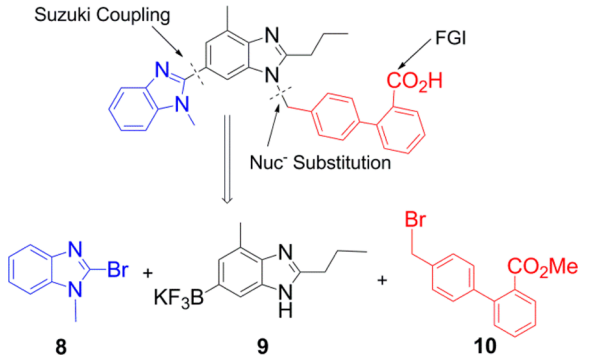
dibenzimidazole moiety; however, this process still suffers from a rather low overall yield.[14] Other groups have taken advantage of cross-coupling reactions to build a formylated biphenyl fragment, avoiding the intricate and low-yielding preparation of **7** used in the original synthesis by substituting a reductive amination approach for the alkylation step.[15−17] Bypassing this alkylation reaction is no longer necessary because affordable analogs of bromide **7** are now commercially available. Notably, none of these modifications represent a significant departure from the original synthetic strategy nor have they remedied the major shortcomings associated with the formation of the dibenzimidazole component of the molecule.

This convergent synthesis of telmisartan entails the assembly of three major subunits: two differentially substituted benzimidazole derivatives and a biphenyl-2-carboxylic acid synthon (Scheme 2). Our strategy provides for the use of a

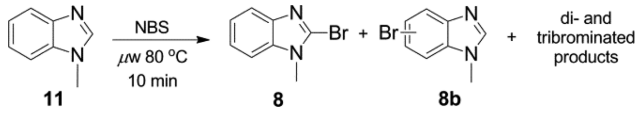
Scheme 2. Retrosynthetic Analysis of Telmisartan



Suzuki cross-coupling reaction to form a new carbon−carbon bond between advanced isolated intermediates. The lack of a convenient and economical preparation of bromobenzimidazole **8** has apparently precluded consideration of this approach until now. The biphenyl moiety is introduced via direct *N*-alkylation with commercially available methyl 4′-bromomethyl-biphenyl-2-carboxylate (**10**), followed by a saponification to the desired carboxylic acid. This approach provides a more efficient assembly of the target molecule, while avoiding the harsh reaction conditions associated with the previous synthetic methods.

Initial efforts focused on preparation of **8**, a strategic element in the Suzuki coupling reaction. Starting with commercially available 1-methylbenzimidazole (**11**), we were able to identify reaction conditions to selectively brominate the imidazole ring with *N*-bromosuccinimide (NBS). While benzimidazoles can be susceptible to bromination at multiple sites[18] resulting in the formation of a mixture of mono-, di-, and tribrominated byproducts, our major challenge was to identify conditions by which bromination could be achieved exclusively at the 2-position in high yield. A solvent screen of microwave-assisted reactions revealed that dichloromethane (DCM), methanol, dimethylformamide (DMF), and diethyl ether yield mainly undesired mixtures of byproducts (Table 1, entries 1−4), but tetrahydrofuran (THF) affords essentially complete conversion to the desired product (entry 5). Similar selectivity trends were observed during solvent screening under conventional reaction conditions (Supporting Information, Table S1), and we were able to achieve an isolated yield of 93% with the THF under reflux conditions. To our knowledge, this is the first example of a selective and scalable bromination of 1-methylbenzimidazole

Table 1. Bromination of 1-Methylbenzimidazole[a]



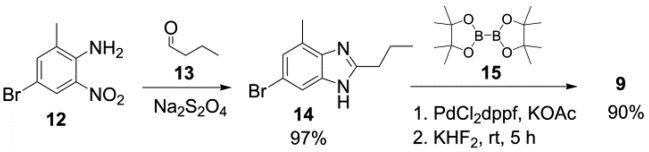
entry	solvent	8[b]	8b[b]	di- and tribromination[b]
1	DCM	0	0	100
2	DMF	0	8	92
3	MeOH	0	12	88
4	Et_2O	0	27	73
5	THF	100	0	0
6[c]	THF	93[d]	0	0

[a]**11** (0.76 mmol), NBS (2.3 mmol), 4 mL of solvent. [b]% Conversions determined by GC-MS. [c]Reaction ran under reflux for 1 h. [d]Isolated yield.

at the 2-position and was an essential element of our convergent strategy. Although compound **8** is available commercially, the cost is prohibitive. This procedure provides an effective and affordable route to **8**, and it is likely that this strategy will find utility in the preparation of other benzimidazole adducts in the future.

In order to establish the necessary precursors for a Suzuki-based approach to the dibenzimidazole core of telmisartan, we elected to prepare the trifluoroborate salt **9** starting from commercially available 4-bromo-2-methyl-6-nitroaniline (**12**). Compound **12** could be easily converted to benzimidazole **14** in a single step. This reductive cyclization, provoked by introducing *n*-butyraldehyde (**13**) in the presence of sodium dithionite,[14] produced **14** in 97% isolated yield (Scheme 3).

Scheme 3. Synthesis of Compound 9



This approach represents a significant improvement over the originally reported method: benzimidazole formation can be completed in a single step, compared to the problematic three-step sequence (amidation, reduction, and cyclization) of Ries et al.[10] Moreover, sodium dithionite provides an effective and inexpensive alternative to the palladium catalyst typically used for reduction of the nitro group. Avoiding palladium in this case is particularly beneficial, as the aryl bromide is susceptible to dehalogenation under Pd-catalyzed hydrogenation conditions.[19]

Benzimidazole **14** was then converted to the trifluoroborate salt **9** in two steps with no isolated intermediate. We chose to introduce the boron species as the pinacol ester.[20] The reaction of 6-bromo-4-methyl-2-propylbenzimidazole (**14**) and diboron **15** (2 equiv) at 100 °C for 5 h in the presence of $PdCl_2$dppf (5 mol %) led to the formation of the desired boronic acid pinacol ester. We converted this pinacol boronate directly to the corresponding trifluoroborate salt,[21] as trifluoroborates tend to be significantly more reactive toward Suzuki cross-coupling reactions.[22−24] The yield from this two-step process is 90% from benzimidazole **14**. Isolation of trifluoroborate **9** is straightforward, as it can be precipitated out of the reaction mixture in pure form.

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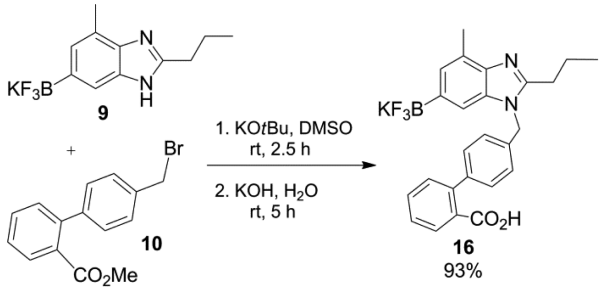
Most of the previous telmisartan syntheses employed a common strategy in which the dibenzimidazole moiety was prepared first, followed by the installation of the biphenyl group. However, we chose to alkylate benzimidazole **9** prior to the Suzuki reaction in order to avoid an observed side reaction between **8** and **9**.[25] The *N*-alkylation of **9** with bromide **10** was carried out in DMSO under basic reaction conditions (Scheme 4). Notably, we found it necessary to pretreat **9** with potassium

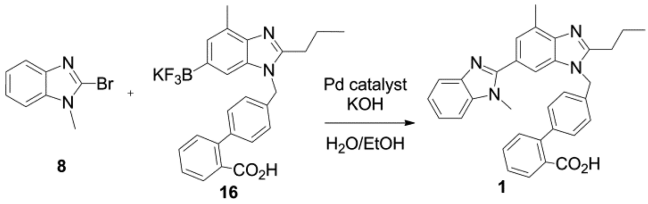
Scheme 4. One-Pot Synthesis of Compound 16



tert-butoxide to avoid the formation of unwanted Williamson ether byproducts. Furthermore, we developed reaction conditions to telescope saponification of the methyl ester with the alkylation step, achieving a 93% yield of **16** over these two chemical steps.

The final coupling reaction of **16** with **8** was carried out under Suzuki cross-coupling reaction conditions[26,27] using $PdCl_2$dppf with KOH in a H_2O/EtOH solvent system. Under atmospheric reflux conditions, the reaction afforded telmisartan in a low to moderate yield (Table 2, entries 1 and 2). In order

Table 2. Suzuki Cross-Coupling To Form Telmisartan[a]



entry	catalyst	conditions	1[b] (%)
1	$PdCl_2$dppf (2 mol %)	reflux, 15 h	36
2	$PdCl_2$dppf (10 mol %)	reflux, 15 h	55
3[c]	$PdCl_2$dppf (2 mol %)	μw 150 °C, 30 min	89
4[c,d]	Pd/G (2 mol %)	μw 150 °C, 20 min	76

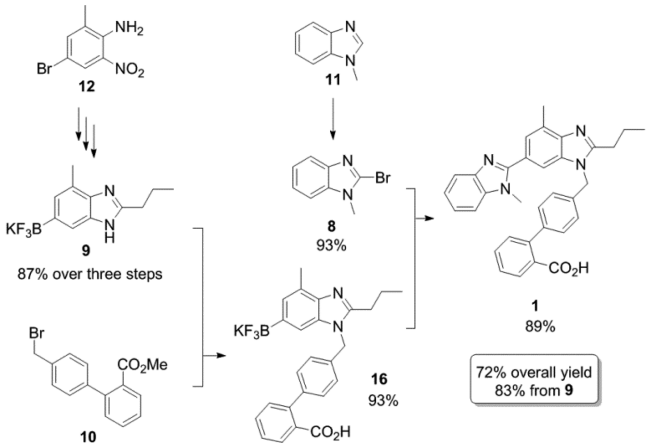
[a]**8** (0.19 mmol), KOH (0.57 mmol), 4 mL of H_2O/EtOH (1:1 mixture). [b]Isolated yield. [c]Reactions were carried out under microwave irradiation at 150 °C, generating a pressure of 18 atm inside the microwave tube. [d]Pd/G catalyst was recycled an additional 2 times affording 68% and 62% isolated yields, respectively.

to achieve higher temperatures with this same solvent system, reactions were then run under elevated pressure using microwave heating. Using this strategy, reaction times were significantly reduced, and isolated yields showed some improvement. We then applied a factorial design of experiment approach in order to identify the set of reaction parameters that would maximize yield while minimizing catalyst loading (Table S2). Optimized Suzuki reaction conditions (Table 2, entry 3) generated telmisartan in 89% isolated yield using only 2 mol % catalyst. We expect that similar results can be achieved under elevated pressures with conventional heating; these studies are currently underway. Other homogeneous catalyst systems were screened; however, $PdCl_2$dppf proved to be the most effective (Supporting Information, Table S3).

In related work, we have recently developed a method to produce highly active Pd nanoparticles supported on graphene (Pd/G).[28] These materials demonstrate remarkable catalytic activity and recyclability in a wide range of Suzuki cross-coupling reactions. Thus, we were interested in evaluating this catalyst system for the key step of our telmisartan synthesis. Preliminary experiments using just 2 mol % of Pd/G under microwave irradiation conditions led to the formation of the desired product with 76% isolated yield (Table 2, entry 4). The palladium content in this final product was lower than that of a sample from the corresponding homogeneous reaction, although both samples are below the USP limits for pharmaceuticals (Supporting Information, Table S4). Furthermore, the catalyst was recycled for two further reactions under the same conditions without appreciable reduction in isolated yield. We are currently evaluating the use of this catalyst system for optimization of both batch and continuous processes for the assembly of telmisartan.

A concise and convergent synthesis of the antihypertensive drug telmisartan has been achieved (Scheme 5). With an overall

Scheme 5. Convergent Synthesis of Telmisartan



yield of 72%, our strategy represents a significant improvement over the highest yield reported previously[9] (50%). Our approach features an efficient Pd-catalyzed Suzuki reaction between two intact benzimidazole moieties as the final reaction step, enabled by the development of a regioselective bromination of 1-methylbenzimidazole. In addition, the harsh reaction conditions that have plagued the commercial route have been avoided and, with only four isolated intermediates in the longest linear sequence, the number of unit operations has been greatly reduced. Our synthetic route also illustrates the potential of graphene-supported Pd nanoparticles (Pd/G) as an alternative catalytic source for cross-coupling reactions. Finally, our strategy has a very efficient endgame, as each step to assemble telmisartan from the key synthons is high-yielding (83% over the final three steps, from trifluoroborate **9**). From a broader perspective, dibenzimidazoles represent an important class of pharmacophores, and this report describes a selective and straightforward method for the preparation of these privileged structures.

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EXPERIMENTAL SECTION

2-Bromo-1-methylbenzimidazole (8). 1-Methylbenzimidazole (**11**) (5.0 g, 37.8 mmol) and *N*-bromosuccinimide (20.2 g, 113.5 mmol) in 200 mL of THF were heated under reflux for 1 h. The solvent was removed by a rotary evaporator, and the residue was recrystallized from EtOAc yielding **8** (7.4 g, 93%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 7.77 (d, 1H), 7.65 (d, 1H), 7.39 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 138.2, 135.4, 131.5, 124.8, 124.7, 117.0, 112.3, 33.0; HRMS (ESI-QTOF): m/z Calcd for $C_8H_7N_2Br$ + H^+: 210.9871; found: 210.9862.

6-Bromo-4-methyl-2-propylbenzimidazole (14). *n*-Butyraldehyde (**13**) (3.1 mL, 34.6 mmol) was added to a 250 mL flask containing 4-bromo-2-methyl-6-nitroaniline (**12**) (4.0 g, 17.3 mmol) and sodium dithionite (18.1 g, 103.9 mmol) in 80 mL of 50% MeOH in H_2O. The reaction was stirred at reflux for 5 h. The methanol was removed via rotary evaporator. To the remaining aqueous solution, an additional 40 mL of water were added and the mixture was extracted using EtOAc (3 × 80 mL). The organic layer was dried using magnesium sulfate. After filtration, the organic layer was removed via rotary evaporator and the resulting solid was dried in the oven producing **13** as a white solid (4.3 g, 97%). ^{1}H NMR (DMSO-d_6) δ 7.47 (s, 1H), 7.08 (s, 1H), 2.77 (t, 2H), 2.47 (s, 3H), 1.79 (m, 2H), 0.95 (t, 3H); ^{13}C NMR (DMSO-d_6) δ 155.7, 124.0, 113.1, 30.5, 20.9, 16.4, 13.6; HRMS (ESI-QTOF): m/z Calcd for $C_{11}H_{13}N_2Br$ + H^+: 253.0340; found: 253.0323.

Potassium (4-Methyl-2-propyl-benzimidazol-6-yl) Trifluoroborate (9). 6-Bromo-4-methyl-2-propylbenzimidazole (**14**) (2.0 g, 7.9 mmol) and bis(pinacolato) diboron (**15**) (4.0 g, 15.8 mmol) were added to a flask along with KOAc (2.3 g, 23.7 mmol) and $PdCl_2$dppf (289 mg, 0.4 mmol). DMSO (20 mL) was added, and the flask was evacuated and placed under nitrogen. The solution was heated at 100 °C for 5 h. The reaction mixture was cooled followed by the addition of 80 mL of H_2O and extracted with EtOAc (3 × 100 mL). The organic layer was combined and concentrated by rotary evaporation. The resulting residue was then taken up in THF (32 mL) and combined with a solution of potassium bifluoride (3.1 g, 39.5 mmol) in H_2O (8 mL). The combined solution was stirred at room temperature for 5 h. Upon removal of the THF, the precipitate was filtered and rinsed using EtOAc, yielding **9** as a white solid (2.0 g, 90%). ^{1}H NMR (DMSO-d_6) δ 7.36 (s, 1H), 7.25 (s, 1H), 3.01 (t, 2H), 2.48 (s, 3H), 1.85 (m, 2H), 0.94 (t, 3H); ^{13}C NMR (DMSO-d_6) δ 152.5, 130.7, 129.3, 121.4, 113.0, 28.5, 21.0, 17.1, 14.0; HRMS (ESI-QTOF): m/z Calcd for $C_{11}H_{13}N_2BF_3K$ + H^+: 281.0839, found: 281.0826.

Potassium (1-(2′-Carboxy-[1,1′-biphenyl]-4-yl)-4-methyl-2-propyl-benzimidazole-6-yl) Trifluoroborate (16). Compound **9** (2.0 g, 7.1 mmol) was added to a solution of KO*t*Bu (2.4 g, 21 mmol) in DMSO (20 mL) and stirred for 30 min at room temperature. Compound **10** (2.2 g, 7.1 mmol) was then added to the reaction mixture and stirred for 2 h at room temperature. A solution of 2 g of KOH (35 mmol) in H_2O (80 mL) was then added to the reaction mixture and stirred for an additional 5 h at room temperature. The solution was adjusted to pH 4 using AcOH, producing a white precipitate. The precipitated material was filtered, rinsed with THF, and then dried, yielding a white solid (3.2 g, 93% yield). ^{1}H NMR (DMSO-d_6) δ 7.22−7.72 (m, 10H), 5.80 (s, 2H), 3.19 (t, 2H), 2.54 (s, 3H), 1.76 (m, 2H), 0.96 (t, 3H); ^{13}C NMR (DMSO-d_6) δ 170.2, 152.8, 141.2, 141.0, 134.8, 132.2, 131.6, 131.2, 129.8, 129.5, 129.4, 128.1, 126.9, 122.2, 112.1, 47.4, 27.3, 21.5, 17.1, 14.1; HRMS (ESI-QTOF): m/z Calcd for $C_{25}H_{23}O_2N_2BF_3K$ + H^+: 491.1520, found: 491.1513.

Telmisartan (1). 2-Bromo-1-methyl-benzimidazole **8** (40 mg, 0.19 mmol) and **16** (97.6 mg, 0.20 mmol) were combined with KOH (31.9 mg, 0.57 mmol) and 2 mol % $PdCl_2$dppf (2.8 mg, 0.004 mmol) in a 1:1 mixture of H_2O and EtOH (4 mL). The solution was heated using microwave irradiation, in a sealed tube, with stirring for 30 min at 150 °C. Temperature was monitored using an IR temperature sensor. The solution was filtered through Celite. To the filtrate, 10 mL of H_2O were added, and the pH was adjusted to 4 using AcOH. The resulting precipitate was filtered and dried in an oven producing telmisartan (86.7 mg, 89% yield). ^{1}H NMR ($CDCl_3$) δ 8.41 (d, 1H), 8.04 (d, 1H), 7.00−7.52 (m, 12H), 5.43(s, 2H), 3.76 (s, 3H), 3.16 (t, 2H), 2.73 (s, 2H), 2.02 (m, 2H), 1.18 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 158.2, 155.7, 145.2, 144.5, 143.3, 142.7, 137.2, 136.2, 135.6, 135.3, 132.1, 131.9, 131.0, 130.6, 130.4, 129.0, 128.8, 125.2, 124.9, 124.8, 123.5, 121.4, 113.0, 111.0, 50.5, 33.5, 31.7, 24.1, 18.6, 15.8; HRMS (ESI-QTOF): m/z Calcd for $C_{33}H_{30}O_2N_4$ + H^+: 515.2447, found: 515.2468.

Procedure for Preparation of Pd Nanoparticles Supported on Graphene (Pd/G). Pd nanoparticles supported on graphene (Pd/G) was prepared according to the procedure developed previously.[28] Graphite oxide (100 mg) and the palladium nitrate (194 μL of 10 wt % in 10 wt % HNO_3, 99.999%) were sonicated in deionized water until a yellow dispersion was obtained. The solution was placed inside a conventional microwave after adding 100 μL of the reducing agent hydrazine hydrate. The microwave oven (Emerson MW8119SB) was then operated at full power (1000 W), 2.45 GHz, in 30 s cycles (on for 10 s, off, and stirring for 20 s) for a total irradiation time of 60 s. The yellow solution of Pd nitrate-graphite oxide changed to a black color indicating the completion of the chemical reduction to graphene. The Pd/G nanoparticles were separated by using an Eppendorf 5804 centrifuge operated at 5000 rpm for 15 min and dried overnight under vacuum.

Procedure for Suzuki Cross-Coupling Reaction Using Pd/G and Recycling the Heterogeneous Catalyst. 2-Bromo-1-methylbenzimidazole **8** (20 mg, 0.094 mmol) was dissolved in a mixture of 2 mL of H_2O/EtOH (1:1) and placed in a 10 mL microwave tube. To this were added **16** (48.8 mg, 0.099 mmol) and potassium hydroxide (21.3 mg, 0.38 mmol). The palladium on graphene catalyst (Pd/G) (2.5 mg, 1.9 μmol) was then added, and the tube was sealed and heated under microwave irradiation (250 W, 2.45 MHz) at 150 °C for 20 min. Upon the completion of the reaction period, the reaction mixture was diluted with 2 mL of 10 mg/mL KOH in EtOH and centrifuged to remove the solid catalyst. The EtOH/KOH washing was repeated twice to ensure the complete dissolution of the product from the surface of the catalyst. The solution was decanted, and the solvent was partially concentrated in *vacuo*. After adjusting the pH of the remaining solution to 4 using AcOH, the precipitated telmisartan product was isolated by filtration and dried in the oven (76% isolated yield). In the case of recycling the Pd/G nanoparticles, the solid catalyst was removed by centrifugation and added to the next reaction mixture using fresh reagents as indicated above. The reaction solution was heated in the microwave at 150 °C for 20 min and the same purification was applied, affording telmisartan with an isolated yield of 68% and 62% in the second and third reactions, respectively.

ASSOCIATED CONTENT

Supporting Information

Spectral data and additional scheme and tables. 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.

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