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Suppression of a Palladium-Mediated Homocoupling in a Suzuki Cross-Coupling Reaction. Development of an Impurity Control Strategy Supporting Synthesis of LY451395

William D. Miller,* Andrew H. Fray, John T. Quatroche, and Christa D. Sturgill

Eli Lilly and Company, Chemical Process Research and Development, Indianapolis, Indiana 46285-4813, U.S.A.

Abstract:

Described herein is the development of a control strategy resulting in exclusion of a persistent impurity (6) formed by a palladium (II)-mediated homocoupling of boronic acid (3) during a Suzuki cross-coupling reaction. Nearly complete suppression of the undesired homocoupling reaction was achieved through two process modifications. Thus, addition of a mild reducing agent, potassium formate, and use of a facile nitrogen subsurface sparge prior to introduction of the catalyst resulted in nearly complete exclusion of homocoupling dimer 6. These modifications apparently minimized the concentration of free Pd(II) in the reaction mixture without causing significant reduction of the oxidative addition product. In addition, use of palladium black as a heterogeneous coupling catalyst rendered the palladium control strategy trivial. Thus, the catalyst was separated from the product solution through use a clarifying filtration, resulting in near quantitative separation of palladium from LY 451395 (5). These conditions were successfully executed in three campaigns using 3-, 5-, 12-, and 22-L glassware.

Introduction

LY 451395 (Scheme 1) is one of a series of AMPA potentiators of interest in treatment of cognitive deficits associated with Alzheimer's disease. We envisioned two significant advantages associated with a convergent synthetic strategy such as that depicted in Scheme 1.[1] Specifically, we noted that this approach would avoid the use of the electrophilic reagents methane sulfonyl chloride and isopropyl sulfonyl chloride late in the sequence. In addition, we anticipated that formation of the biaryl linkage late in the sequence might facilitate the development of an acceptable impurity control strategy, since the potential for a stepwise accumulation of structurally similar biaryl impurities would be avoided. An apparent disadvantage of this approach is that it requires at least one palladium-mediated reaction late in the sequence, thus potentially presenting the challenge of separating the catalyst from the product. A second disadvantage that was not initially anticipated involved generation of dimer **6** (Figure 1) as a single persistent impurity that was produced at unacceptable levels.

Discussions and Results

At the outset, we established three critical success factors related to product quality for the proposed route. We desired to establish a control strategy that would afford the active pharmaceutical ingredient containing less than 2% total of related substances, no more than 0.5% of a single impurity, and less than 10 ppm palladium. We were intrigued by the potential of using a late-stage cross-coupling mediated by a heterogeneous palladium catalyst or precatalyst such as palladium on carbon, palladium black, or palladium acetate.[2] We anticipated that use of a heterogeneous catalyst might facilitate a near quantitative separation of the catalyst and product by a simple clarifying filtration of the reaction product solution subsequent to reaction completion.

Our initial attempts using palladium acetate demonstrated that a heterogeneous palladium catalyst would promote the desired cross-coupling. In addition to the desired product (**5**), we observed formation of a major persistent impurity and several other impurities that were efficiently rejected upon crystallization of the product. As shown in Table 1, HPLC analysis[3] of five couplings conducted under similar conditions revealed formation of dimer **6** in variable amounts. We also observed significant variability in the time required to drive the reactions to completion.

A sample of dimer **6** was isolated from an impure sample of LY 451395, and the structure was confirmed by comparison (^{1}H NMR, MS) to that of a sample prepared by unambiguous synthesis as shown in Scheme 2.

Given the conditions of the coupling, two pathways for formation of this impurity seemed possible (Scheme 3). An obvious pathway would involve a normal Suzuki coupling between boronic acid **3** and aryl iodide **1** (Ar−M + Ar−X). In principle, the synthetic sequence in Scheme 1 presents an opportunity for formation of dimer **6** during formation of aryl boronate **2**, where Ar−X (**1**), Ar−M (**2** or **3**), and palladium are simultaneously present. However, in agreement with the findings of Masuda,[4] we did not observe formation of dimer **6** during this step. In addition, analysis of arylboronic acid **3** also revealed that aryl iodide **1**[5] was not present in amounts required to produce dimer **6** via a normal

* To whom correspondence should be addressed. E-mail: miller_william_d@lilly.com.

(1) Preparative procedures for aryl iodide **1** and aryl iodide **4** have been previously disclosed, See Gardner, J. P.; Miller, W. D. U.S. Patent 6,984,756 B2, 2001.

(2) (a) Beletskaya, I. P. *Pure Appl. Chem.* **1990**, *69*, 471−476. (b) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, 59, 5034−5037, (c) Marck, G.; Villager, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277−3280.

(3) The following HPLC conditions were used for all analyses referenced herein. Column: 4.6 mm × 250 mm SB-phenyl 5 μm at 35 °C. Mobile phase: 46% 0.1 % trifluoroacetic acid in water, 54% 0.1% trifluoroacetic acid in acetonitrile, 1.5 mL/min isocratic. Detection: UV at 260 nm.

(4) Murata, M.; Masuda, Y.; Watanabe, S. *J. Org. Chem.* **1997**, *62*, 6458−6459.

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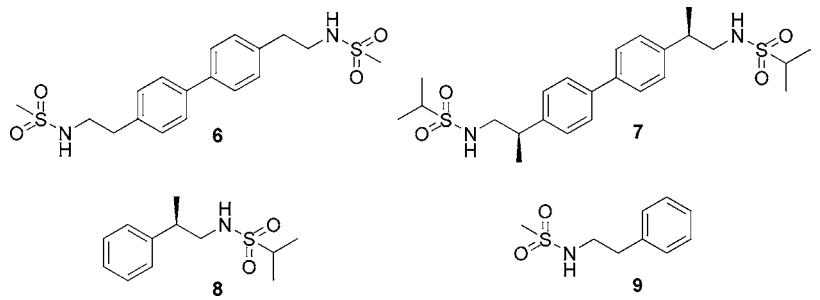


Figure 1. **Impurities generated during Suzuki cross-coupling of 3 and 4.**

Scheme 1. **Preparation of LY 451395 via Suzuki coupling**

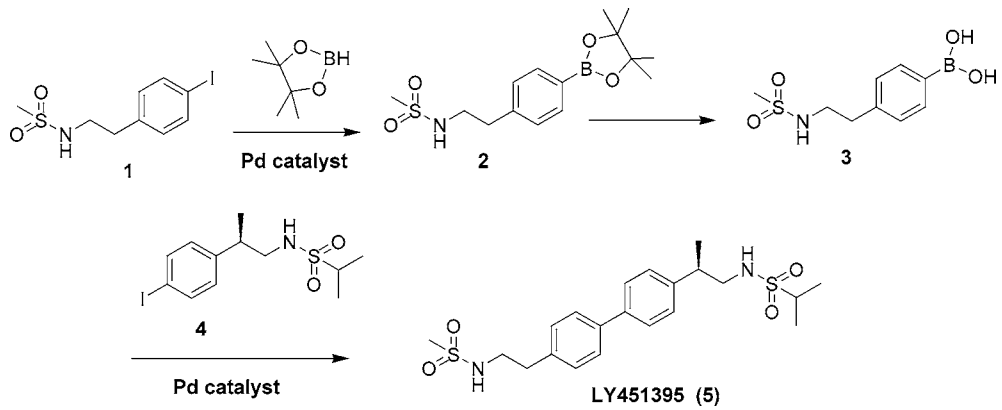


Table 1. **Cross-coupling results using palladium acetate**

entry	$Pd(OAc)_2$ (mol %)	dimer **6** (%)	time to reaction completion (h)	reactor inerting
1	1.6	4.1	46	brief N_2 headspace sweep
2	1.5	2.9	96	brief N_2 headspace sweep
3	2.2	3.1	24	brief N_2 headspace sweep
4	1.1	1.5	24	brief N_2 headspace sweep
5	1.1	2.6	24	brief N_2 headspace sweep

Suzuki cross-coupling during the final Suzuki cross-coupling step. We therefore concluded that the second pathway involving boronic acid homocoupling must be primarily responsible for generating dimer **6**. Accordingly, we focused on gaining a better understanding of this pathway, with the aim of modifying the Suzuki coupling conditions to inhibit formation of dimer **6**.

We found several references relevant to this problem,[6] but taken together, the references presented a somewhat ambiguous view of boronic acid homocoupling. However, these references presented a modest level of agreement on two points.

1. Exclusion of oxygen is necessary to suppress homocoupling regardless of the actual mechanism.

2. Homocoupling of boronic acids can proceed via a stoichiometric reaction between Pd(II) and a boronic acid, resulting in formation of a symmetrical biaryl and Pd(0).

We initiated additional experimentation to elucidate the influence of these factors on formation of dimer **6** in our cross-coupling reaction. As evidenced by the entries in Table 2, we observed that both factors exerted a significant influence on formation of dimer **6**. Entry 1 revealed that use of a 5% Pd on carbon catalyst resulted in approximately one-half the dimer **6** content of similar reactions using $Pd(OAc)_2$. In order to assess the potential for additional improvement through exclusion of oxygen from the reaction mixture, we vacuum degassed the reaction mixtures and used nitrogen backfill to return the reactor to atmospheric pressure. We repeated this procedure an additional two times prior to introduction of the palladium catalyst. Entry 2 reveals that this modification afforded an additional significant decrease in formation of dimer **6**. Finally, we observed that use of palladium black appeared to offer an additional decrease in formation of dimer **6** as evidenced by entries 3 and 4.[7]

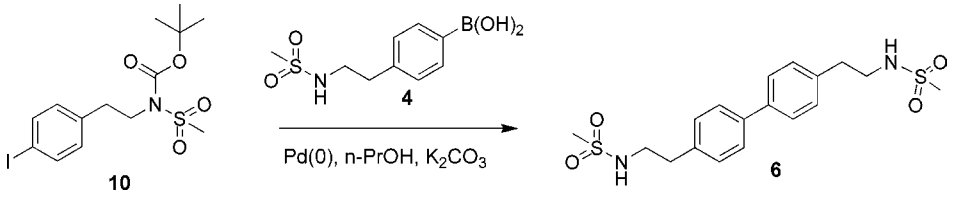
Although these modifications appeared to fulfill our initial goals with respect to control of related substances, we sought to identify additional modifications that might further suppress dimer **6** formation. It occurred to us that addition of a mild reducing agent to the reaction mixture might provide for rapid reduction of free palladium (II) species that might be produced by reaction with other oxidants present in the reaction mixture. One might anticipate potential liabilities associated with this approach, including reduction of the desired oxidative addition complex **(Ar′Pd(II)−X)** derived from aryl iodide **4** prior to transmetalation. This pathway

(5) Analysis of boronic acid **3** also excluded other impurities that might function as synthetic equivalents of aryl iodide **1**.

(6) (a) Moreno-Manas, M.; Pajuelo, F.; Plexats, R. *J. Org. Chem*. **1995**, *60*, 2346−2351. (b) Wallow, T. I.; Novak, B. M. *J. Org. Chem*. **1994**, *59*, 5034−5037. (c) Marck, G.; Villager, A.; Buchecker, R. *Tetrahedron Lett*. **1994**, *35*, 3277−3280. (d) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, G. M. *Chem. Commun*. **1994**, 2395.

(7) In principle, palladium black and palladium on carbon should give equivalent results, as long as the palladium on carbon is free of oxygen and palladium (II). In our view, use of palladium black offered a number of practical advantages so we did not further pursue the use of palladium on carbon. We found the task of equipment cleanup after using palladium black to be relatively simple and also found that essentially quantitative separation of the catalyst from the product to be fairly trivial. Numerous lots of palladium black from Aldrich and Englehard were evaluated and found to be equivalent for our application.

Scheme 2. **Unambiguous synthesis of dimer 6**



Scheme 3. **Possible pathways to dimer 6**

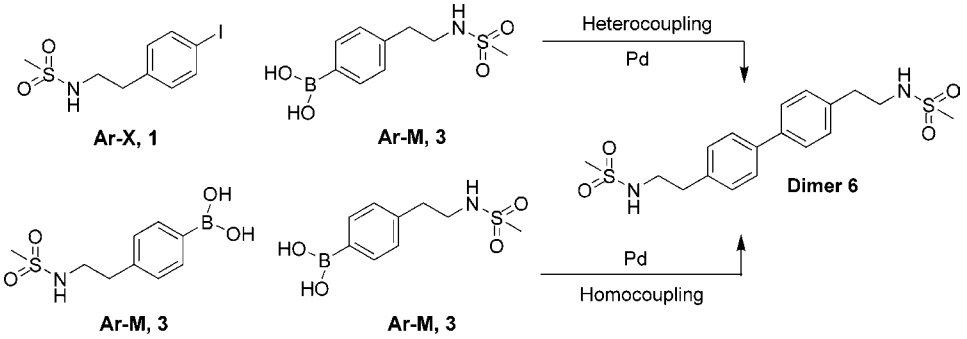


Table 2. **Additional studies on suppression of dimer 6 formation**

entry	mol % Pd	% dimer **6**	O_2 control procedure	comments
1	1.1% Pd/5% C	1.4	brief headspace sweep	significant decrease in dimer **6**
2	1.1% Pd/5% C	0.5	vac/N_2 backfill	significant decrease in dimer **6**
3	1% Pd black	0.3	vac/N_2 backfill	significant decrease in dimer **6**
4	1% Pd black	0.3	vac/N_2 backfill	repeat

Table 3. **Results of cross-coupling reactions using KCO_2H**

entry	Pd	dimer **6** (%)	O_2 control	ppm Pd (ICP) (ppm)	comments
1	Pd black	0.06	vac/N_2 backfill	0.5	potassium formate added
2	Pd black	0.07	vac/N_2 backfill	9.8	potassium formate added
3	Pd black	0.07	vac/N_2 backfill	not analyzed	potassium formate added
3	Pd black	0.08	vac/N_2 backfill	not analyzed	potassium formate added
5	Pd black	0.07	vac/N_2 backfill	not analyzed	potassium formate added
6	Pd black	0.07	vac/N_2 backfill	not analyzed	potassium formate added

would potentially afford either **8 (Ar′−H)** or chiral dimer **7 (Ar′−Ar′)** (Figure 1).[8]

An initial survey of mild reducing agents revealed that addition of potassium formate further suppressed formation of dimer **6**. As indicated in Table 3, we observed that this additional modification to the reaction conditions reproducibly suppressed dimer **6** to a level below 0.1%. Not surprisingly, we also observed formation of approximately 10% **8 (Ar′−H)** and approximately 0.5% chiral dimer **7** in these reaction mixtures; however, we observed that both of these impurities were efficiently rejected during crystallization of LY 451395.

A proposed catalytic cycle showing formation of the various reaction products consistent with these observations is depicted in Figure 2.

Thus, Figure 2 shows that two equivalents of boronic acid **3 (Ar−M)** might undergo a sequential transmetalation with free palladium (II) followed by reductive elimination affording dimer **6 (Ar−Ar)** and palladium (0). Reoxidation of palladium (0) by dissolved oxygen[9] or other oxidants[10] could provide completion of a catalytic cycle for this pathway. A combination of the rigorous deoxygenation and addition of potassium formate to the reaction mixture presumably ensured that essentially all of the free palladium is present as Pd\(0), which would then undergo the desired oxidative addition with **4 (Ar′−X)**. The utility of this approach requires that the pathways leading to reductive dehalogenation and formation of **7 (Ar′− Ar′)** be relatively slow processes. Formation of dimer **6** by a stoichiometric palladium (II)-mediated homocoupling of boronic acid **3** was demonstrated experimentally.

ICP-MS analysis of the isolated product from two early reactions using these modifications revealed very low residual palladium after filtration of the reaction mixtures through 0.8 μm glass fiber media prior to crystallization.

(8) Bamfield, P.; Quam, P. M. *Synthesis* **1978**, *7*, 537−538.

(9) For examples of catalytic palladium (II) reactions using molecular oxygen for reoxidation, see: Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298−5300 and Rönn, M.; Bächvall, J.-E.; Andersson, P. G. *Tetrahedron. Lett.* **1995**, *36*, 7749−7752.

(10) The ease with which palladium (0) is oxidized necessitates consideration of the potential impact of minor organic and inorganic impurities in the starting materials, reagents, and solvents used in the cross-coupling.

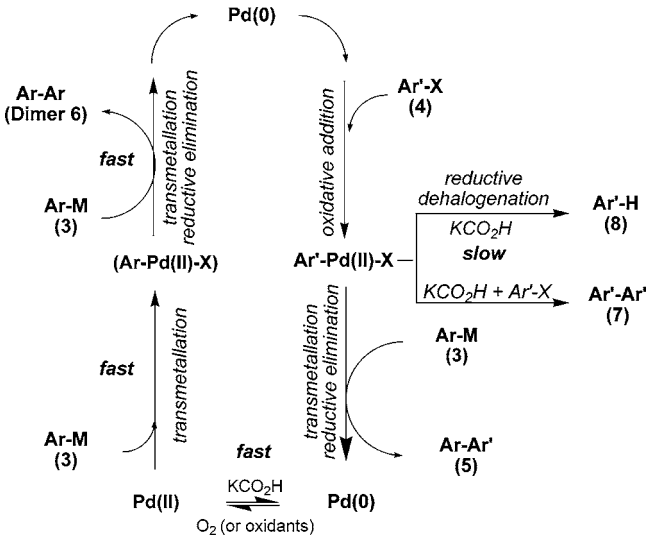


Figure 2. **Catalytic cycle for formation of observed reaction products.**

Table 4. **Percentages of dimer 6 vs dissolved oxygen at $t = 0$**

entry	ppm O_2	% dimer **6**
1	0.5	0.071
2	2.2	0.18
3	3.3	0.18

Facile Deoxygenation. Having established the important role of dissolved oxygen in promoting formation of dimer **6**, we sought to directly measure[11] and identify an upper maximum limit for dissolved oxygen. Three one-liter-scale experiments were completed in order to assess the efficiency and feasibility of deoxygenation using subsurface sparging. In these experiments, a mixture of water and 1-propanol was saturated with oxygen by subsurface addition of air, resulting in measurement of 8.3, 8.7, and 8.6 ppm oxygen. Nitrogen gas was then introduced at a rate of 0.5 standard cubic feet per hour (SCFH) resulting in reduction of dissolved oxygen to less than 0.5 ppm in 2.5 min. Thus, at 0.5 SCFH for 2.5 min, a total of 0.02083 standard cubic feet (SCF) of nitrogen was required to deoxygenate 1 L of solution. On this basis, we calculated that for 1000 L of reaction a purge rate of 30 SCFH of nitrogen for 41.7 min would be required to reduce the oxygen level from saturation to less than 0.5 ppm. Measurement of the recovered solution volume indicated that solvent loss due to evaporation was approximately 0.8%. We concluded that deoxygenation via subsurface sparging would be efficient and practical for large-scale work.

In order to establish the maximum tolerable limit of dissolved oxygen we initially ran three experiments in which nitrogen sparging was interrupted prior to complete removal of dissolved oxygen. These experiments indicated that essentially complete deoxygenation was required in order to minimize formation of dimer **6** as indicated in Table 4.

These process modifications appeared adequate to suppress formation of dimer **6** by homocoupling of the boronic acid, but there remained a need to prevent residual aryl iodide **1** from entering the key coupling reaction as an impurity in boronic ester **3**. We observed that purging aryl iodide **1** from boronic ester **2** by crystallization was problematic. For this reason, we elected to submit boronic ester **2** to hydrolysis and formal isolation prior to the Suzuki cross-coupling reaction. Boronic acid **3** was freely soluble in water upon addition of base. This rendered quantitative removal of neutral organics such as iodide **1** and dimer **6**[12] by liquid−liquid extraction trivial.

These modifications to the cross-coupling reactions collectively enabled the manufacture of LY 451395 that met our product quality critical success factors. The manufacture of API supporting preclinical toxicology studies and Phase I clinical trials was executed in three campaigns, and the couplings were run in 3-, 5-, 12-, and 22-L glassware. The technical grade product resulting from each cross-coupling reaction was isolated, and the individual lots were combined for recrystallization to provide a single lot from each campaign. Table 5 summarizes the scale and excellent run-to-run consistency afforded by the process. Table 6 demonstrates the near quantitative separation of palladium by means of a simple clarifying filtration in the final step of this process.

Table 5. **Campaign 1−3 Suzuki coupling results**

entry	campaign	scale (L)	dimer **6** (%)	mass of LY451395 (**5**) generated (g)
1	1	3	0.01	110
2	1	3	0.01	102
3	1	3	0.01	101
4	1	3	0.01	101
5	1	3	0.01	101
6	1	3	0.02	101
7	2	5	0.03	132
8	2	22	0.03	532
9	2	22	0.03	818
10	2	22	0.03	776
11	2	22	0.05	760
12	3	5	<0.1[a]	112
13	3	12	<0.1[a]	538
14	3	12	<0.1[a]	541

[a] Quantitation by limit test.

Table 6. **Campaign summary API (5)**

entry	campaign	Pd levels (ppm)	TRS (%)	LY 451395 produced (g)
1	1	<2	0.29	536
2	2	<1	0.20	2400
3	3	<1	0.10	1080

(11) An ICM model 31250 dissolved oxygen probe and meter was used for laboratory work. Devices such as Metler-Toledo InPro 6800/6900 or InPro 6800 Gas may be found more suitable for manufacture of clinical material.

(12) Formation of dimer **6** during the boronation reaction has never been observed. However, early work revealed that using ligated palladium precatalysts such as [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium (II) or bis(triphenylphosphine) palladium (II) diacetate during the boronation step resulted in a propensity for formation of dimer **6** upon exposure of boronic acid **3** to base. Later work using palladium black as a heterogeneous catalyst minimized but did not entirely eliminate this potential. Boronic acid **3** derived from palladium black boronations have low (less than 10 ppm) but detectable levels of palladium.

Conclusion

The control strategy for a Suzuki coupling performed as a final step is described. Suppression of the homocoupling of an aryl boronic acid leading to a persistent dimer (**6**) was achieved by the combination of two key process modifications. Thus, it was shown that rigorous exclusion of dissolved oxygen from the reaction mixture could be easily and efficiently achieved by subsurface sparge with nitrogen. Furthermore, dimer **6** suppression was additionally promoted by the introduction of potassium formate to the Suzuki reaction, which may have played the role of a mild reducing agent that did not block the catalytic cycle. These modifications apparently minimized the concentration of free Pd(II) in the reaction medium without causing significant reduction of the oxidative addition product. And finally, use of a heterogeneous catalyst, palladium black, enabled the essentially quantitative separation of palladium from the desired cross-coupling product by filtration of the reaction mixtures through a 0.8 μm glass fiber filter. These conditions were successfully executed in three campaigns using 3-, 5-, 12-, and 22-L glassware.

Experimental Section

Generalized Procedure for Deoxygenation of Aqueous 1-Propanol Using Subsurface Nitrogen Sparging. An apparatus was assembled consisting of a 1-L round-bottom flask equipped with a mechanical stirrer, 1/4 in. Teflon dip tube, dissolved oxygen probe, and a reflux condenser supplied with −5 °C cooling fluid. A mixture of 441 mL of deionized water and 559 mL of 1-propanol was charged to the flask. The mixture was held at 25 °C and stirred while compressed air was added subsurface. Nitrogen gas was then introduced into the rapidly stirred solution through the 1/4 in. Teflon dip tube at 0.5 SCFH until the oxygen meter indicated less than 0.5 ppm dissolved oxygen.

***N*-[2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]ethyl]methanesulfonamide (2).** Aryl iodide **1** (977 g, 3.00 mol) and triethylamine (914 g, 9.03 mol) were added to acetonitrile (5.9 L). The resulting mixture was stirred under nitrogen and cooled to 14 °C. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (pinacol borane), (929 g, 7.26 mol) was added slowly via cannula to the mixture over 75 min, allowing a controlled evolution of hydrogen and warming to 25 °C. Upon completion of the addition, acetonitrile (0.20 L) was used to rinse the transfer line. The reaction mixture was stirred at 25−30 °C for about 3 h, after which time the reactor headspace was flushed with nitrogen in order to remove hydrogen from the flask and reaction mixture. Agitation was stopped, and a Teflon transfer tube was inserted below the liquid surface. A suspension of palladium black[13] (9.6 g, 0.09 mol) in acetonitrile (0.10 L) was added to the reaction mixture though the transfer line. Additional acetonitrile (0.4 L) was used to rinse the palladium from the flask and transfer line. Agitation was resumed, and the mixture was warmed to 75 °C under nitrogen for 24 h. The reaction mixture was cooled to 21 °C, and deionized water (115 g, 6.40 mol) was slowly added over 24 min with cooling to permit a controlled release of hydrogen while maintaining 21−28 °C. After the addition was complete, the reactor headspace was flushed with nitrogen for 45 min to remove hydrogen. The reaction mixture was filtered through Celite (750 g) to remove the catalyst, and the reaction flask and filter cake were rinsed with acetonitrile (4.0 L). The filtrate was concentrated to a weight of 3038 g by distillation under reduced pressure, and the concentrate was diluted with ethyl acetate (2.9 L). The mixture was cooled to 2 °C over 2 h and was filtered to remove precipitated triethylammonium iodide. The filter cake was rinsed with ethyl acetate (2 L) which had been prechilled to 0 °C. The filtrate was extracted twice with water (3 L) and once with brine (4.0 L). Sodium sulfate (803 g) was added to the organic phase, and the suspension was stirred at 25 °C for 40 min. The suspension was filtered, and the filtrate was concentrated under reduced pressure to 2.44 kg. Heptane (5 L) was added to the concentrate, and the solution was slowly cooled to 2 °C over 30 min. The resulting precipitate was recovered by filtration, and the filter cake was rinsed with heptane (3.5 L) which was precooled to 2 °C. The collected solids were vacuum dried at 40 °C, affording aryl boronate **2** (656 g, 67.2% yield) from aryl iodide **1**. ^{1}H NMR ($CDCl_3$, 500.0 MHz): δ 7.78 (d, 2H, J = 8), 7.23 (d, 2H, J = 8), 4.15 (t, 1H, J = 6.5), 3.42 (doublet of triplets, 2H), 2. 90 (t 2H), 2.83 (s, 3H), 2.83 (s, 3H).1.35 (s, 12H).

[4-[2-[(Methylsulfonyl)amino]ethyl]phenyl]boronic Acid (3). Aryl boronate **2** (0.655 kg, 2.01 mol) was added to a mixture of water (3.7 L) and concentrated (48%) HBr (0.865 L, 7.64 mol). The reaction mixture was warmed to 85 °C and stirred for 11 h under nitrogen and then was cooled to 20 °C. The pH of the reaction mixture was adjusted to 10.8 by addition of 2.0 N sodium hydroxide (4.9 L, 9.8 mol), and the resulting solution was extracted three times with *tert*-butyl methyl ether (1.8 L). The aqueous phase was stirred with activated carbon (87.7 g) at 25 °C for 1 h under nitrogen. The suspension was filtered, and the filter cake was rinsed with water (1 L). The filtrate was acidified slowly with 24% HBr (0.435 L) to a pH of 2.7. The resulting suspension was cooled to 0−5 °C, and the precipitate was recovered by filtration. The product filter cake was rinsed with cold water (2.0 L) and vacuum dried at 40 °C, affording boronic acid **3** (0.412 kg, 1.69 mol) in 84% yield. ^{1}H NMR (acetone-d_6/D_2O, 300.0 MHz): δ 7.81 (d, 2H, J = 8), 7.26 (d, 2H, J = 8), 3.268 (t, 2H, J = 7) 2. 827 (s 3H), 2.814 (t, 4H, J = 7).

Independent Synthesis of *N*,*N*′-([1,1′-Biphenyl]-4,4′-diyldi-2,1-ethanediyl)-bis-methanesulfonamide (6). A mixture of 1-propanol (134 mL), water (104 mL), arylboronic acid **3** (12.2 g, 0.0500 mol, 1.0 equiv), Boc-protected aryl iodide **10** (22.3 g, 0.0525 mol, 1.05 equiv), K_2CO_3 (11.3 g, 0.0820 mol, 1.64 equiv), and palladium black (53 mg, 0.5 mmol, 0.010 equiv) was heated to reflux at 89 °C for 2.5 h. The mixture was cooled to 50 °C, and the resulting suspension was filtered. The filter cake was dissolved in DMSO (150 mL), and the suspension was filtered to remove palladium black. The filtrate was poured slowly into water (750 mL) and stirred for 15 min. The precipitate was

(13) Alternatively, palladium dichloride or palladium diacetate may be used, since these are immediately reduced to palladium (0) by excess pinacol borane.

recovered by filtration and added to a mixture of trifluoroacetic acid (150 mL) and dichloromethane (150 mL) for 2 h. Dichloromethane was removed by distillation under reduced pressure, and the precipitate was recovered by filtration. The filter cake was suspended in water (100 mL) for 10 min, filtered, and dried under vacuum, affording dimer **5** (9.9 g) in 50% yield as a white powder. ^{1}H NMR (DMSO-d_6, 300.0 MHz): δ 7.57 (d, 4H, J = 8.4), 7.31 (d, 4H, J = 8.1), 7.08 (t, 2H, J = 6), 3.18 (app q, 4H, J = 7.2), 2.83 (s, 6H), 2.79 (t, 4H, J = 7.5).

Unoptimized Cross-Coupling Procedure Producing a Mixture of 5 and 6. *2-Propanesulfonamide,* N-*[(2R)-2-[4′-[2-[(Methylsulfonyl)amino]ethyl][1,1′-biphenyl]-4-yl]propyl] (5).* A mixture of aryl iodide **4** (1.51 g, 4.11 mmol, 1.0 equiv), potassium carbonate (0.630 g, 4.56 mmol, 1.1 equiv), decolorizing carbon (0.10 g), and palladium acetate (0.010 g, 0.045 mmol, 0.011 equiv) in 1-propanol (10 mL) and water (3 mL) was stirred and heated to 80 °C under nitrogen. A solution of arylboronic acid **3** (1.00 g, 4.11 mmol, 1.0 equiv) in 1-propanol (10 mL) was added by syringe pump to the heated aryl iodide solution at a rate of 1 mL h^{-1}. After 24 h, the reaction was cooled to ambient temperature. The mixture was diluted with EtOAc (25 mL) and was suction filtered through a Hyflo filter-aid followed by an EtOAc rinse (2 × 25 mL). The filtrate was concentrated in vacuo to a paste that was partitioned between EtOAc (50 mL) and 10% aqueous K_2CO_3. The organic phase was extracted with 10% aqueous K_2CO_3 (2 × 25 mL) and saturated brine (1 × 25 mL), was dried (Na_2SO_4), and was filtered. The filtrate was concentrated to15 mL and diluted with heptane (15 mL). The resulting precipitate was filtered, and the filter cake was rinsed with 1:1 EtOAc/heptane (1 × 10 mL) followed by heptane (1 × 10 mL), affording 1.27 g (70.4%) of impure LY 451395 as an off-white solid. HPLC analysis of the solid revealed 97.3% LY 451395 **(5)** and 2.6% dimer **6**.

Isolation of Dimer 6 from a Mixture of 5 and 6. A sample of impure **5** (0.5 g) containing dimer **6** was stirred in $CHCl_3$ (5 mL) at 25 °C for 18 h. The suspension was filtered through Celite, and the filter cake was rinsed twice with $CHCl_3$ (10 mL). The filtrates were discarded, and the cake was rinsed with DMSO-d_6 (3 × 0.75 mL). ^{1}H NMR (DMSO-d_6, 300.0 MHz) analysis of the filtrate was consistent with the structure of authentic dimer **5** produced by independent synthesis: δ 7.57 (d, 4H, J = 8.4), 7.31 (d, 4H, J = 8.1), 7.08 (t, 2H, J = 6), 3.18 (app q, 4H, J = 7.2), 2.83 (s, 6H), 2.79 (t, 4H, J = 7.5).

2-Propanesulfonamide, *N*-[(2*R*)-2-[4′-[2-[(Methylsulfonyl)amino]ethyl][1,1′-biphenyl]-4-yl]propyl] (LY 451395 Optimized Procedure). Deionized water (2.8 L), potassium formate (0.0526 kg, 0.620 mol), potassium carbonate (0.303 kg, 2.19 mol), boronic acid **3** (0.325 kg, 1.34 mol), aryl iodide **4** (0.501 kg, 1.36 mol), and 1-propanol (3.0 L) were combined and stirred at 24 °C to give a clear solution. Nitrogen was introduced by subsurface addition for 30 min until measurement of the exit gas indicated depletion of oxygen. A suspension of palladium black (1.45 g, 0.0136 mol) in water was added to the reaction solution, and deoxygenation of the resulting mixture by subsurface nitrogen addition was continued for an additional 15 min. The reaction apparatus was vented to a stream of nitrogen and was heated to reflux at 90 °C for approximately 8 h. The reaction mixture was cooled to 80 °C, and the agitation was stopped, allowing separation of a lower aqueous phase. A closed stainless steel filter containing 0.8 μm glass fiber media was equipped with a Teflon inlet and outlet lines. The inlet line was inserted into the lower aqueous phase, and the lower aqueous phase was filtered to recover palladium black, cooled, neutralized, and discarded. In the same way, the upper organic phase was filtered to remove palladium black, and the filtrate was diluted with deionized water (0.65 L) and cooled to 4 °C. The resulting precipitate was collected by filtration, rinsed with cold 1-propanol (1.3 L), and deionized water (1.3L), and then vacuum dried at 45 °C, affording technical grade **5** (0.542 kg, 1.24 mol) in 92.2% yield. A mixture of technical grade **(5)** (0.360 kg) and acetone (1.98 L) was warmed to 45 °C, and the solution was diluted with water (1.62 L), while maintaining a temperature of 45 °C. The mixture was cooled to 5 °C over 2.75 h and stirred for an additional 1.75 h. The resulting precipitate was collected by filtration, rinsed with a cold mixture of acetone (0.660 L) and water (0.660 L), and vacuum dried at 45 °C, affording 335 g LY 451395 in 93.0% yield from technical grade LY 451395. ^{1}H NMR ($CDCl_3$, 300.0 MHz): δ 7.54 (dd, 4H, J = 2.1, 9), 7.29 (dd, 4H, J = 2.1, 9), 4.38 (t, 1H, J = 6.3), 4.00 (m, 1H), 3.44 (app q, 2H, J = 6.6), 3.36 (dd, 1H, J = 5.7, 6.9), 3.26 (m, 1H), 3.05 (m, 2H), 2.92 (app t, 2H, J = 6.6), 2.86 (s, 3H), 1.33 (d, 3H, J = 7.8), 1.31 (d, 3H, J = 7.2), 1.27 (d, 3H, J = 6.9).

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