Mechanistic Studies of the Suzuki Cross-Coupling Reaction

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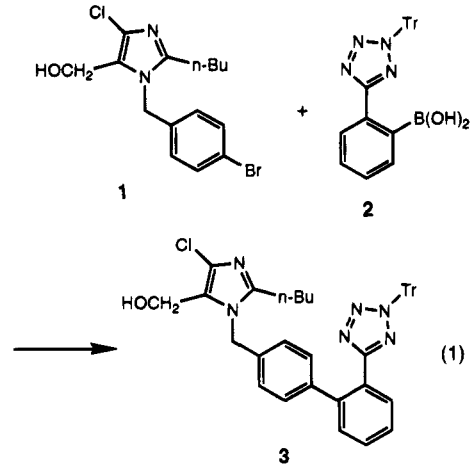
The key step in the synthesis of the drug substance losartan is a palladium-catalyzed cross-coupling reaction of an aryl bromide and a boronic acid. The reaction scheme was defined in kinetic studies using HPLC, and computer simulation served to depict the time dependence of the concentrations of palladium species, which were not observed experimentally. Two catalyst poisons were identified and characterized. One was an isomeric impurity of the aryl bromide; the other formed in the reaction mixture upon hydrolysis of the boronic acid and two of its impurities.

Introduction

Cross-coupling reactions of unsaturated (aryl, alkynyl, or alkenyl) carbon centers, catalyzed by transition metals, have become powerful tools in organic synthesis. Palladium-catalyzed couplings of unsaturated halides or sulfonates with organostannanes (the Stille reaction[1]) and with boronic acids or esters (the Suzuki reaction[2]) are among the most widely used reactions of this genre. The necessary use of tin in stoichiometric amount in the Stille reaction makes it less attractive than the Suzuki reaction for applications in the fine chemical or pharmaceutical industry.

Relatively little is known about the mechanistic details of these reactions, despite their popularity. In studies of the Stille reaction of vinyltributyltin and iodobenzene, Farina and Krishnan[3] found that the transmetalation step of the catalyst cycle is rate-determining and that ligand dissociation from palladium is pivotal in the transmetalation. Likewise, Negishi *et al.*[4] found that the transmetalation is rate-determining in the palladium-catalyzed coupling of (*E*)-1-octenylzinc chloride and iodobenzene. Amatore *et al.*[5] studied the first step of the coupling reaction in depth, namely the oxidative addition, and showed that the coordinately unsaturated Pd(0)-$(PPh_3)_2$ is the likely catalytic species. Fitton and Rick[6] found oxidative addition of aryl iodides to tetrakis-(triphenylphosphine)palladium rapid at room temperature whereas aryl bromides required heating to about 80 °C and aryl chlorides were unreactive up to 135 °C. This study suggested that the halide leaving group might dictate which step of the catalyst cycle is rate-determining.

Losartan potassium, the first of a new class of drugs called angiotensin II receptor antagonists, was developed for treatment of high blood pressure and heart failure. The key step in the synthesis is a heterogeneous Suzuki cross-coupling reaction of aryl bromide **1** and boronic acid **2** to make trityl losartan **3**, eq 1. While an empirical study of reaction parameters led to a well-defined process of high yield, more detailed understanding of the process reaction, and of cross-coupling reactions in general, was desired. In this article we describe mechanistic studies demonstrating that water and base are required to activate the boronic acid, that the rate-determining step depends on the identity of the aryl halide, and that low-level impurities of both **1** and **2** cause catalyst poisoning.



Catalyst Preparation

Tetrakis(triphenylphosphine)palladium(0) is generally used as catalyst for Suzuki reactions in the laboratory. Its cost and oxidative lability made it unsuitable for a larger-scale process, however, and Pd^0 was generated *in situ*. The catalyst was prepared by heating a THF solution of 0.05 M triphenylphosphine and 0.0125 M Pd^{II}-$(OAc)_2$ for 0.5 h at 60 °C (see Experimental Section). HPLC chromatograms of such solutions included sharp peaks of triphenylphosphine and the phosphine oxide and a broad peak thought to be due to palladium species. Some of the triphenylphosphine observed initially disappeared while the phosphine oxide appeared. Thus the oxide was recognized as an oxidation product formed while the palladium was reduced, as described by Amatore *et al.*[5c] This reaction seemed complete in about 3 h at 25 °C, 2 h at 30 °C, or 0.2 h at 60 °C. The stoichiometry was not determined, however, since the phosphine was not all accountable in terms of the phosphine and phosphine oxide peak areas.

The ^1H and ^{13}C spectra of a similar solution prepared using deuterated THF revealed sharp peaks for tri-

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(1) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–24.

(2) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749–1758.

(3) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–95.

(4) Negishi, E.; Takahashi, T.; Baba, S.; van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393–2401.

(5) (a) Amatore, C.; Pfluger, F. *Organometallics* **1990**, *9*, 2276–82. (b) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375–84. (c) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009–3013.

(6) Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287–291.

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phenylphosphine oxide and broad peaks, believed to indicate complexation, for the phosphine and for acetate or acetic anhydride. The redox reaction was written as follows, although acetic anhydride was not positively identified.

$$Pd(OAc)_2 + nPPh_3 \rightarrow Pd(PPh_3)_{n-1} + OPPh_3 + Ac_2O \quad (2)$$

Normally the catalyst was prepared using 4 mol of triphenylphosphine per mole of palladium as described above. At least 3 mol of phosphine were required to avoid precipitation of Pd black during the coupling reaction, and slower coupling resulted when more phosphine was used. For example, coupling proceeded at one-third the normal rate using 6 mol of phosphine instead of 4 mol. This is consistent with literature indicating that deligation of palladium is required to generate the active catalyst.[5]

$$Pd(PPh_3)_4 \underset{+PPh_3}{\overset{-PPh_3}{\rightleftharpoons}} Pd(PPh_3)_3 \underset{+PPh_3}{\overset{-PPh_3}{\rightleftharpoons}} Pd(PPh_3)_2 \quad (3)$$

The same coupling reaction took place at about half the normal rate when unheated 0.0125 M solution of tetrakis(triphenylphosphine)palladium in THF was used instead of the preheated solution of the phosphine and $Pd(OAc)_2$. The slower rate was consistent with the presence of more triphenylphosphine, none of which was converted to the phosphine oxide as in the catalyst preparation, but of course the mixture also lacked products of the catalyst preparation introduced normally.

Rate Effects of Changing the Initial Composition

The prepared catalyst solution in THF was added to a slurry of **1**, **2**, potassium carbonate, and water in diethoxymethane, and the resulting mixture, in which the carbonate was undissolved, was stirred at 75 °C. Normally the process coupling reaction was carried out starting with 0.25 M **1** and 0.30 M **2**, with 2.5 mol of potassium carbonate and 3.0 mol of water per mole of **1**, and with 1 mol % of palladium relative to **1**. Aliquots of the heterogeneous mixture and the solution phase, withdrawn at a given reaction time, were the same in regard to **1**–**3** using HPLC, i.e., the main components were completely dissolved.

At first we focused on the water and the base in the reaction mixture, realizing that Suzuki reactions are usually performed with a hydroxylic solvent such as water or an alcohol and with a base present. Kinetic data for **3** appearing in a run at process conditions and in runs at varied conditions are shown in Figure 1. With twice the normal, process amount of carbonate present initially, coupling stopped at about 50% conversion but continued when water equimolar to the extra carbonate was added at 3 h reaction time, as if the undissolved carbonate held a certain amount of water, making it unavailable in the solution phase. Coupling proceeded normally in another run with the double charge of carbonate and the equimolar water present initially. With half the process amount of water present initially, coupling stopped at about 35% conversion but continued when the rest of the process amount was added. And with half the normal amount of carbonate, coupling stopped at about 65% conversion but continued when the rest of the carbonate was added. The rates observed upon adding water or carbonate nearly matched the normal rates at the same conversions. Thus the catalyst seemed to remain essentially intact during the delays of several hours.

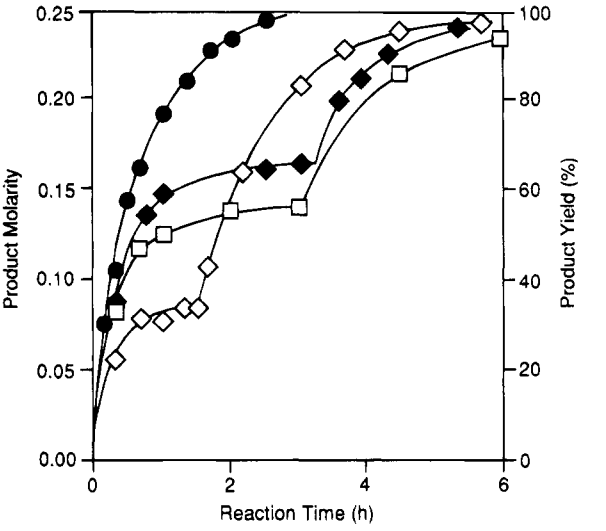


Figure 1. Coupling rate effects of K_2CO_3 and water. Key: (●) process reaction conditions; (□) double charge of K_2CO_3 with water added at 3 h; (◇) half charge of water with more water added at 1.5 h; (◆) half charge of K_2CO_3 with more K_2CO_3 added at 3.2 h.

These results suggested that the overall stoichiometry requires 2 mol each of water and carbonate. ^{11}B NMR studies indicate that arylboronic acids behave as Lewis acids in alkali, adding hydroxide to form the tetrahedral anion.[7] We reasoned that 1 mol of water and 1 mol of carbonate are required initially to activate the boronic acid, and that another of each is used to neutralize boric acid, the coupling reaction byproduct, eqs 4 and 5. Kuivila showed that the anion is 10^6 times more reactive than the neutral boronic acid in electrophilic reactions.[8] This suggests that **2a** is the reactive species rather than **2** in the present reaction.

$$\underset{\mathbf{2}}{ArB(OH)_2} + K_2CO_3 + H_2O \rightarrow \underset{\mathbf{2a}}{ArB(OH)_3^-K^+} + KHCO_3 \quad (4)$$

$$B(OH)_3 + K_2CO_3 + H_2O \rightarrow B(OH)_4^-K^+ + KHCO_3 \quad (5)$$

The coupling rate was unchanged when $K_2CO_3 \cdot {}^3/_2H_2O$ was substituted for anhydrous K_2CO_3 and water, i.e., hydration of K_2CO_3 was rapid relative to the coupling reaction.

Comparable coupling rates were observed using sodium carbonate or cesium carbonate instead of potassium carbonate, but practically no coupling occurred using potassium bicarbonate, a weaker base. This is consistent with the necessity to form **2a** to initiate coupling. Assuming the pK_a of **2** to be close to that of benzeneboronic acid (pK_a 8.8 in aqueous solution[9]), carbonate (pK_a 10.3) is a base of sufficient strength to form **2a**, but bicarbonate (pK_a 6.35) is too weak.

(7) Dewar, M. J. S.; Jones, R. *J. Am. Chem. Soc.* **1967**, *89*, 2408–2410.
(8) Kuivila, H. G.; Reuwer, J. F.; Margravite, J. A. *Can. J. Chem.* **1963**, *41*, 3081–3090.
(9) Edwards, J. O.; Sederstrom, R. J. *J. Phys. Chem.* **1961**, *65*, 862–863.

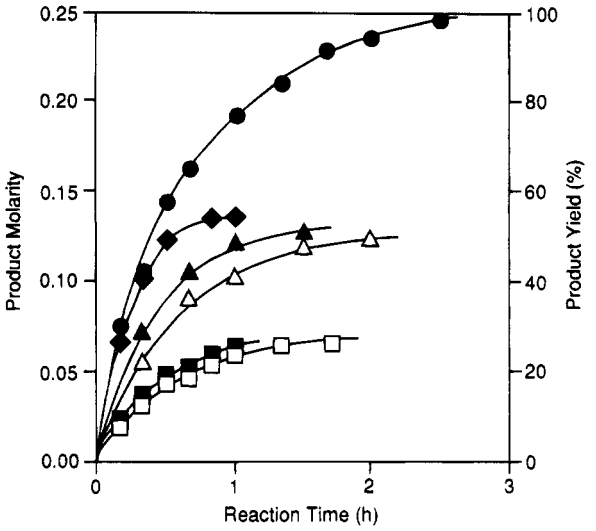
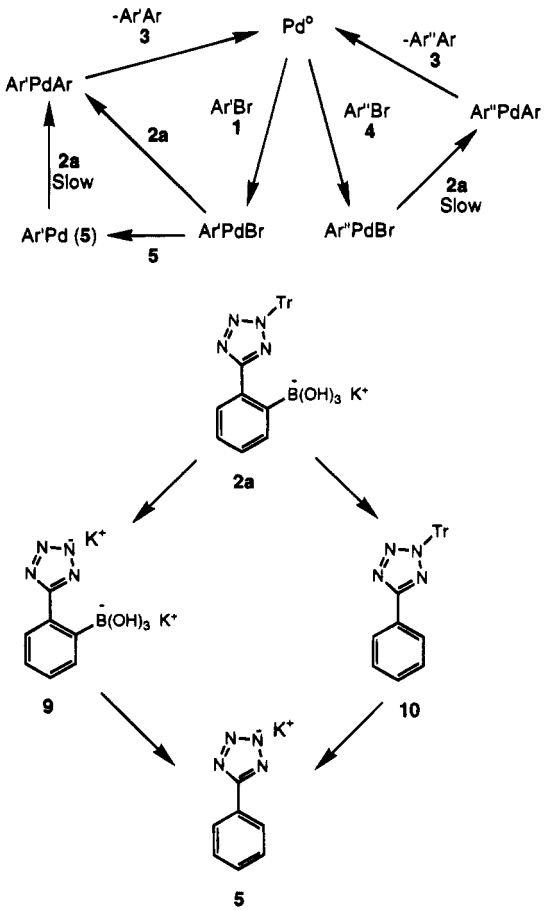


Figure 2. Coupling rate effects of **1** and **2**. Key: (●) process reaction conditions; (△) half charge of **1**; (▲) half charges of both **1** and **2**; (□) quarter charge of **1**; (■) quarter charges of both **1** and **2**; (◆) half charge of **2**.

Scheme 1



According to the literature[4] the catalyst cycle includes oxidative addition of Pd^0 to aryl bromide **1**, transmetalation of the resulting Ar'PdBr and **2a** to form biaryl palladium species Ar'PdAr, and reductive elimination of product Ar'Ar (Scheme 1, top left). The oxidative addition was found to be rate-determining since the coupling rate was strongly dependent on the concentrations of the catalyst and **1** but nearly independent of **2**, as follows.

In kinetic runs at reduced catalyst concentrations, otherwise at process conditions, the coupling rate varied approximately in proportion to the catalyst concentration. These data reflected catalyst poison, discussed later. And in runs at reduced initial concentration of **1**, otherwise at process conditions, the coupling rate was found proportional to the concentration of **1**, Figure 2. When the initial concentration of **1** was normal and the concentration of **2a** was halved, making it the limiting reagent, coupling began at about the normal rate but then became somewhat slower. (The other runs in Figure 2, with reduced initial concentrations of both **1** and **2a**, are discussed later in the context of catalyst poisons.)

The catalyst cycle was probed further in kinetic runs using the same boronic acid and an aryl iodide, *p*-iodotoluene, whose oxidative addition should be much faster.[6] (The coupled product of this reaction was available from previous studies in these laboratories.[10]) Indeed, in runs at different initial concentrations the coupling rate was found proportional to the concentrations of the catalyst and **2a** but independent of the concentration of iodotoluene, i.e., the transmetalation was found rate-determining. Thus the slow step of this Suzuki reaction was shown to depend on the identity of the halide. The slow step using aryl bromide **1** was the oxidative addition; that using iodotoluene was the transmetalation.

A Mathematical Model

A catalyst cycle consisting of slow oxidative addition and transmetalation steps and relatively rapid reductive elimination was simulated in order to visualize the catalyst species, that were not observed experimentally. Simultaneous differential equations describing the concentrations of the reactants were integrated numerically using the method of Gear.[11] The oxidative-addition rate constant k_1 was adjusted to 1000 M^{-1} h^{-1} to fit the initial coupling rate of **1**, and k_1 was made very large for the coupling of iodotoluene. The transmetalation rate constant k_2 was adjusted to 10 000 M^{-1} h^{-1} to fit iodotoluene kinetic data, and the same k_2 value was assumed for the coupling of **1**.

The concentrations of Pd^0 and Ar'PdBr, calculated for the coupling of **1**, conformed to a steady state approximation, eq 6.

$$k_1[Pd^0][\mathbf{1}] = k_2[Ar'PdBr][\mathbf{2a}] \qquad (6)$$

It follows from eq 6 that the percentage of palladium present as Pd^0 depends on the rate constant ratio k_1/k_2 and the concentration ratio [**1**]/[**2a**].

$$\frac{100[Pd^0]}{[Pd]_{total}} = 100\Big/\left\{1 + \frac{k_1[\mathbf{1}]}{k_2[\mathbf{2a}]}\right\}$$

$$\text{where } [Pd]_{total} = [Pd^0] + [Ar'PdBr] \qquad (7)$$

At process conditions the initial concentration ratio is 0.25/0.30 and, according to eq 7, 92% of the palladium is present as Pd^0 and 8% as Ar'PdBr. The percentage of Ar'PdBr is a measure of impedance due to the transmetalation. As coupling proceeds, the concentration ratio decreases to zero, and the calculated [Pd^0] approaches $[Pd]_{total}$, 0.0025 M at 1% catalyst charge, Figure 3.

With half charge of **2**, however, the initial concentration ratio is 0.25/0.15, and 14% of the palladium is

(10) Shuman, R. F.; King, A. O.; Anderson, R. K. U.S. Patent 5,039,814, 1991.

(11) Gear, C. W. *Numerical Initial Value Problems in Ordinary Differential Equations*; Prentice-Hall: Inglewood Cliffs, NJ, 1971.

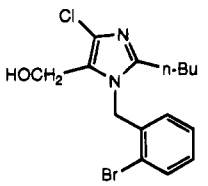
present as Ar'PdBr. As coupling proceeds with **1** in excess, the concentration ratio increases and the calculated [Pd^0] goes to zero. Consequently, the calculated appearance of **3** lags that with the full charge of **2**, like the kinetic data plotted in Figure 2.

Simulations of the coupling of **1** with k_2 values either larger or smaller than the fitted value differed from the kinetic data. With k_2 moderately larger, the lag disappeared. And k_2 values moderately smaller meant that the palladium was largely present as Ar'PdBr initially. Then the calculated coupling rate, unlike the observed rate, became strongly dependent on [**2a**]. Thus the assumption that the transmetalation reactivities of aryl bromide **1** and iodotoluene are about the same was confirmed, and dissociative transmetalation as shown in eq 8 seemed unlikely.

$$ArPdL_2X \underset{+X^-}{\overset{-X^-}{\rightleftharpoons}} ArPdL_2^+ \xrightarrow{Ar'B(OH)_3^-} ArPdL_2Ar' \quad (8)$$

Catalyst Poisons

Since the catalyst was used in small amount relative to the reactants, minor components of the reaction mixture interacting adversely with the catalyst retarded the coupling significantly. The identification of **4** and **5** (Scheme 1) as catalyst poisons was important in process development, and kinetic studies of the poisons defined the minimum amount of catalyst needed for a reliable process.



4

Compound **4** was an isomeric impurity of **1** amounting to about 0.1%. In kinetic runs with 1 or 3% of **4** added relative to **1**, otherwise at process conditions, the coupling of **1** and **2** began normally but became very slow, Figure 4. In a duplicate run with 3% of **4** added, a second catalyst charge was introduced at 4 h reaction time. Then coupling resumed at about the rate observed at the same conversion without added **4**, indicating that the reaction had slowed for lack of catalyst. (The kinetic data showed that 0.1% of impurity **4** was tolerable with the 1% catalyst charge.)

The oxidative addition step of the catalyst cycle was observed separately using aryl bromide in only moderate excess to the catalyst. Using 0.005 M **1** (only 2 mol per mole of palladium) and no **2**, otherwise at process conditions initially, the oxidative addition to Ar'PdBr was completed in 1 h at 75 °C. This was indicated by the disappearance of **1** equimolar to the palladium. Then 0.004 M **2** was added; it disappeared and equivalent **3** formed in about 15 min.

(12) **6**: δ_H 7.97 (m, 1H), 7.52 (m, 2H), 7.33 (m, 3H), 7.28–7.21 (om, 9H), 7.14 (td, J = 8.5, 2.0, 1H), 6.97 (dd, J = 7.5, 1.2, 1H), 6.92 (m, 6H), 6.57 (d, J = 7.7, 1H), 4.97 (d, J = 17.2, 1H), 4.89 (d, J = 17.2, 1H), 4.12 (d, J = 13.5, 1H), 4.00 (d, J = 13.5, 1H), 2.32 (m, 2H), 1.50 (m, 2H), 1.22 (m, 2H), 0.80 (t, J = 7.4, 3H); δ_C 163.7, 148.5, 141.1 (3C), 139.3, 139.0, 134.5, 130.5, 130.3, 130.2, 130.1 (6C), 128.6, 128.4 (3C), 128.3, 128.2, 127.8 (6H), 127.1, 126.7, 125.4, 124.7, 83.3, 52.6, 46.3, 29.7, 26.4, 22.3, 18.4, 13.7.

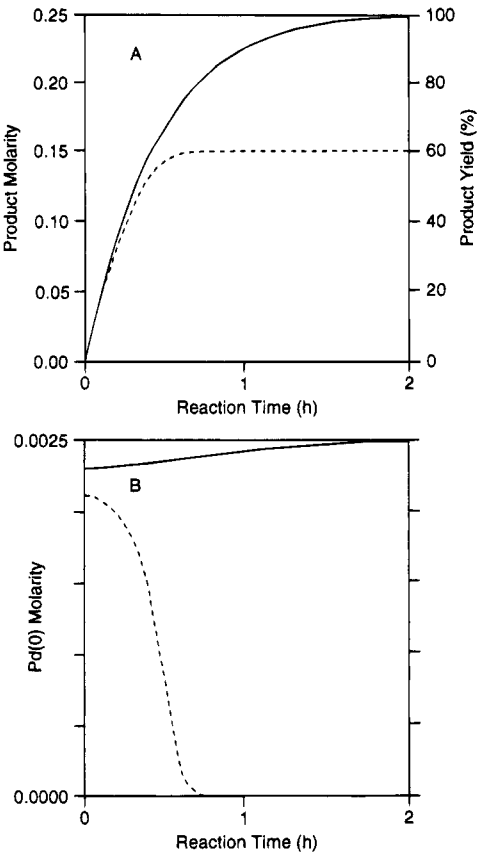


Figure 3. Calculated concentrations of product (A) and Pd^0 (B) in coupling reactions of **1** and **2**. Key: (—) process reaction conditions; (– – –) half charge of **2**.

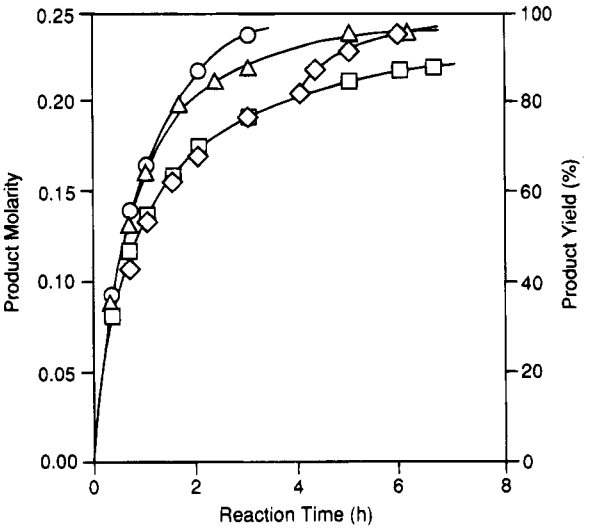


Figure 4. Coupling rate effect of **4**. Key: (○) 0.1% of **4** present in **1**; (△) 1% of **4** added; (□) 3% of **4** added; (◇) 3% of **4** added with more catalyst added at 4 h.

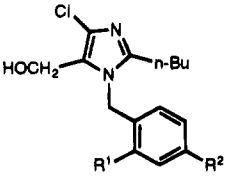
Using **4** instead of **1**, the oxidative addition rate was about the same, but the subsequent coupling of **2** was slow. Compound **2** disappeared and **6**[12] appeared at the same rate, with a half-life of 10 h (scheme 1, top right). The equal rates of disappearance of **2** and appearance of **6** indicated slow transmetalation followed by relatively rapid reductive elimination. Product appearance would lag reactant disappearance if the reductive elimination were slow. Using the less bulky (*p*-methoxyphenyl)-boronic acid instead of **2**, after oxidative additions of **1** and **4**, the coupled products **7**[13] and **8**,[14] respectively, each

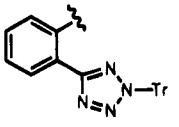
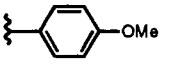
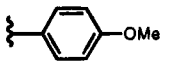
Table 1. HRMS Data

compound	empirical formula	calculated for MH^+	found MH^+
6	$C_{41}H_{37}N_6OCl$	665.2796	665.2769
7	$C_{22}H_{25}N_2O_2Cl$	385.1683	385.1668
8	$C_{22}H_{25}N_2O_2Cl$	385.1683	385.1681

formed in 15 min. Thus the poisoning effect of **4** in the process coupling reaction of **1** and **2** was ascribed to steric hindrance of the transmetalation.

There was no evidence of side reactions. The coupled products were isolated from the reaction mixtures using semipreparative HPLC. The expected structures **6**–**8**,



Compound	R^1	R^2
6		H
7	H	
8		H

consistent with the footnoted NMR data, were confirmed using HRMS, Table 1.

Another poison was indicated by moderate batch-to-batch coupling rate differences of boronic acid **2**, exemplified in runs at normal reaction conditions using batch 1, whose kinetic data are shown in Figures 1 and 2, and the somewhat slower reacting batch 2, Figure 4. The rate difference of batches 1 and 2 was enhanced by reducing the catalyst charge from 1 to 0.25%, so that reaction mixtures contained more poison relative to the catalyst, Figure 5. Also, in runs at 1% catalyst charge with one-half or one-fourth of the normal initial concentration of **1**, the coupling rate was somewhat faster when the initial concentration of **2a** was reduced as well, Figure 2. This might result from lower concentration of a hindering impurity of the boronic acid, with no rate dependence on the concentration of **2a** itself.

The impurities of the boronic acid observed using HPLC were trityl alcohol, the destrityl boronic acid **9**, and the deboronated analogue **10** shown in Scheme 1, and three unknowns. (The boron group and the destrityltetrazole are anionic in the alkaline reaction mixture.)

(13) **7**: δ_H 7.54–7.48 (om, 4H), 7.05 (d, J = 8.3, 2H), 6.98 (d, J = 8.8, 2H), 5.25 (s, 2H), 4.53 (s, 2H), 3.86 (s, 3H), 2.60 (m, 2H), 1.69 (m, 2H), 1.36 (m, 2H), 0.88 (t, J = 7.3, 3H); δ_C 159.4, 148.7, 140.6, 134.4, 133.8, 132.8, 128.1 (2C), 127.3 (2C), 126.3 (2C), 124.7, 114.3 (2C), 55.4, 53.4, 47.3, 29.8, 26.9, 22.5, 13.8.

(14) **8**: δ_H 7.21–7.17 (om, 3H), 7.13–7.04 (om, 2H), 6.86 (m, 2H), 6.80 (d, J = 7.4, 1H), 5.18 (s, 2H), 4.57 (s, 2H), 3.42 (s, 3H), 2.21 (m, 2H), 1.52 (m, 2H), 1.16 (m, 2H), 0.75 (t, J = 7.4, 3H); δ_C 159.2, 148.5, 140.4, 133.8, 132.3, 130.3, 130.1 (2C), 127.9, 127.6, 127.0, 125.6, 125.2, 114.1 (2C), 55.4, 53.0, 45.8, 29.4, 26.6, 22.3, 13.7.

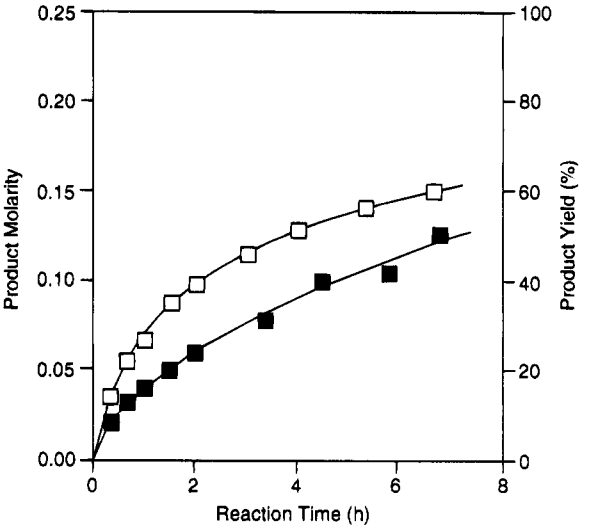


Figure 5. Batch-to-batch rate difference of the boronic acid at 0.25% catalyst charge relative to **1**. Key: (□) batch 1; (■) batch 2.

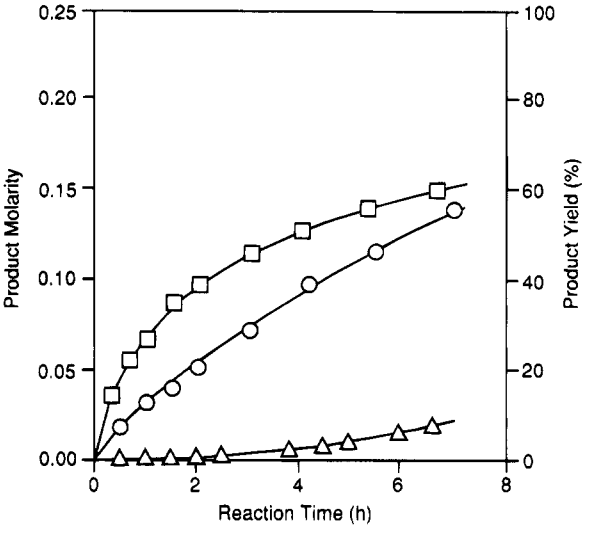


Figure 6. Coupling rate effect of **5** using boronic acid batch 1 at 0.25% catalyst charge. Key: (□) no **5** added; (○) 0.2% of **5** added relative to **2**; (△) 0.8% of **5** added.

Boronic acid batch 2, with apparently more poison than batch 1, contained more trityl alcohol and more **9**, but less of the other impurities. The coupling rate was unchanged when trityl alcohol was added to the reaction mixture. Compound **9**, amounting to 0.2 and 0.4 mol % in batches 1 and 2, respectively, disappeared completely during the first hour of the reaction while equimolar **5** appeared in the solution phase and the coupling rate decreased, Figure 5. Thus **5** became suspect, but possible poisoning by (the unstable) **9** was not ruled out.

Compound **2a** deboronated to **10** at a rate of 1% / h at process conditions, and **5** formed by detritylation of **10**, but more slowly than by deboronation of **9**. Slow detritylation of **2a**, observed in the absence of **1**, increased the concentration of **9** at a trivial rate, Scheme 1.

The poisoning effect of **5** added to reaction mixtures using boronic acid batch 1 is shown in Figure 6. With 0.2% of **5** added relative to **2** (making the sum of **5** and **9** equal to the content of **9** in batch 2), the coupling rate was about the same as that using batch 2, Figure 5. Thus the rate effect of the added **5** accounted for the rate difference of boronic acid batches 1 and 2. Coupling was severely depressed with 0.8% of **5** added.

Losartan, whose structure also includes the anionic tetrazole moiety, formed by slow detritylation of **3** at process conditions. When losartan was added to the coupling reaction mixture instead of **5**, in the same molar amount, the same poisoning effect was observed. Losartan posed no process threat, however, since its yield was below 0.01%, much less than the catalyst concentration of 1%.

Ordinarily coupling began when the catalyst was added last, but the initial coupling rate was unchanged when **1** was added last after the rest of the reaction mixture had aged at 75 °C, or when **2** was added last. So it seemed that poisoning occurred only when all components of the reaction mixture were present, as if **5** poisoned Ar'PdBr or Ar'PdAr but not Pd^0. Accordingly the rate of the oxidative addition was found unchanged by added **5**. In reaction mixtures with 0.005 M **1** (only 2 mol per mole of palladium) and no **2**, otherwise at process conditions initially, **1** equimolar to the palladium disappeared at the same rate in the absence and presence of 0.005 M **5**. Upon adding 0.004 M **2** along with 0.005 M **5** after oxidative addition in the absence of **5**, **2** disappeared slowly ($t_{1/2}$ = 1 h), and **3** appeared at the same rate, indicating slow transmetalation and relatively rapid reductive elimination, Scheme 1. And using the less bulky (*p*-methoxyphenyl)boronic acid instead of **2**, coupling proceeded at the same slow rate, as if the anionic tetrazole ligand rendered Ar'PdBr less reactive toward either boronic acid.

Conclusions

Kinetic data for the Suzuki reaction to make trityl losartan **3** were consistent with a reaction scheme including rate-determining oxidative addition, faster transmetalation, and very rapid reductive elimination. Water and base were found necessary to activate boronic acid **2**. Using an aryl iodide instead of aryl bromide **1**, the transmetalation step was found rate-determining.

Mechanistic studies centered on catalyst poisons **4** and **5**, Scheme 1. Retardation due to **4** seemed to result from steric hindrance of the transmetalation, with the palladium accumulating as Ar''PdBr. Slow transmetalation due to **5** was a more immediate rate effect, ascribed to unfavorable interaction of the tetrazole anion and Pd^{II}.

Experimental Section

Materials. H_3PO_4 (85%) (Fisher certified ACS), MeCN (Fisher HPLC grade), EtOH (USP 200 proof) (Quantum Chemical Corp), and 2,2,4-trimethylpentane (EM Science Omnisolv) were used for HPLC mobile phases.

Catalyst solution was prepared using 99.8% $Pd(OAc)_2$ (Johnson Matthey, Inc), 97–101% PPh_3 (Aldrich Chemical Co), and THF (EM Science Omnisolv). $Pd(PPh_3)_4$ (99%) (Aldrich) was used also.

Coupling reaction mixtures were prepared using diethoxymethane (DEM) 99.7% (Eastman Kodak Co) and K_2CO_3 anhyd powder, −325 mesh, 98+% (Aldrich). Compounds **1**–**3**, **5**, and **10** were available in these laboratories as intermediates of the losartan process.[15] Compound **4** was prepared according to the process for **1**, starting with *o*-bromo(bromomethyl)benzene instead of the *p*-bromo isomer. (*p*-Methoxyphenyl)boronic acid was prepared from (*p*-methoxybromo)benzene according to the literature.[16] Using *p*-iodotoluene (99%) (Aldrich) instead of **1** in the process Suzuki reaction, **2** coupled cleanly to form the expected product described previously.[10] Compound **9** formed readily upon detritylation of **2** in aqueous MeCN solution containing H_3PO_4.

Table 2. Retention Times

compound	t_R, min	compound	t_R, min
9	1.8	*p*-MeC_6H_4I	8.9
p-$MeOC_6H_4B(OH)_2$	2.3	TrOH	10.2
5	2.4	2	10.8
Losartan	2.8	Ph_3P	13.3
1	4.7	3	13.7
4	5.3	6	13.7
Ph_3PO	5.6	10	15.3
7	6.4	product of *p*-MeC_6H_4I and 2	17.6
8	6.4		

Kinetic Runs. Coupling reactions were carried out on a 50-mL scale under nitrogen purge in a jacketed vessel equipped with a mechanical stirrer and a mercury thermometer. The standard procedure with 1% catalyst charge relative to **1** was as follows.

In the catalyst preparation, PPh_3 (0.5 mmol) was dissolved in 10 mL of THF. The solution was degassed to remove O_2, and $Pd(OAc)_2$ (0.125 mmol) was added. The solution was degassed again, purged with N_2, heated at 60 °C for 0.5 h, and cooled to room temperature. The remaining ingredients, normally **1** (12.5 mmol), **2** (15 mmol), anhyd K_2CO_3 (31 mmol), H_2O (40 mmol), and DEM (40 mL), were charged to the reaction vessel, degassed, and purged with N_2. Then the catalyst solution in THF was transferred to the reaction vessel using a syringe, and water was circulated through the jacket from a constant-temperature bath to maintain a reaction temperature of 75 °C. Aliquots of the heterogeneous reaction mixtures were withdrawn periodically while stirring, or aliquots of the solution phase were taken with the stirrer turned off momentarily. The aliquots were dissolved and diluted in aqueous MeCN and analyzed using HPLC.

HPLC. Liquid chromatography was performed using a 250 × 4.6 mm Zorbax SB-phenyl column (DuPont) with a mobile phase gradient composed of 0.1% v/v H_3PO_4 in MeCN and 0.1% aqueous H_3PO_4, delivered at a rate of 2 mL/min and monitored at 225 nm with the column at ambient temperature. The same HPLC system was used to analyze catalyst-preparation solutions or coupling reaction mixtures. Retention times are listed in Table 2.

Products **6**–**8** were isolated from coupling reaction mixtures in milligram amounts for spectroscopic examination using a 250 × 21.4 mm Dynamax Sil column (Rainin) with a mobile phase composed of 2,2,4-trimethylpentane and EtOH. The products were rechromatographed to purities of at least 90 area %.

NMR and HRMS. NMR samples were dissolved in $CDCl_3$. Proton and carbon-13 spectra were recorded on a Bruker AM400 (400.13 MHz ^1H; 100.61 MHz ^{13}C) spectrometer.

High-resolution FAB measurements were performed vs Fomblin Oil (perfluoropolypropylene oxide) by (+)-FAB mass spectrometry with a JEOL HX110A mass spectrometer set at a resolution of 5000. Samples were ionized from a 3-nitrobenzyl alcohol matrix using Xe as the FAB gas.

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