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Observation of Catalytic Intermediates in the Suzuki Reaction by Electrospray Mass Spectrometry

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Electrospray ionization mass spectrometry (ESI-MS) has been used extensively in the characterization of proteins and nucleic acids.[1] Recent studies of stable ionic compounds in solution[2] have included preformed organometallic species and transition-metal complexes.[3] Surprisingly, the technique has been applied directly to a reaction system in only a limited number of studies.[4] We now report the use of ESI-MS to observe transient catalytic intermediates involved in the Pd(0)-catalyzed coupling reaction of arylboronic acids with bromopyridines.

The palladium(0) cross-coupling reaction of aryl halides and arylboronic acids is an important synthetic method.[5,6] Although few mechanistic studies of organoboron compounds have been reported,[7] many other studies employing related organometallic species have led to the generalized catalytic mechanism shown in Figure 1.[8] The proposed cycle involves oxidative addition of the aryl halide to the palladium(0) catalyst, transmetalation of boron for palladium to form a *trans*-diarylpalladium(II) species, isomerization of the *trans* isomer to the *cis*, and reductive elimination of the biaryl, regenerating the catalyst.[9]

The plausibility of this cycle has been previously demonstrated mainly by the synthesis and characterization of organopalladium compounds structurally related to the proposed intermediates. Arylpalladium(II) complexes have been isolated and well characterized.[10] Diarylpalladium(II) species have been observed,[11] although less data are available on these compounds. Elegant studies have identified the reactive compounds by ^{31}P and ^{1}H NMR spectroscopy under carefully chosen conditions.[12] However, the key intermediates in Figure 1 have not been observed directly under reaction conditions.

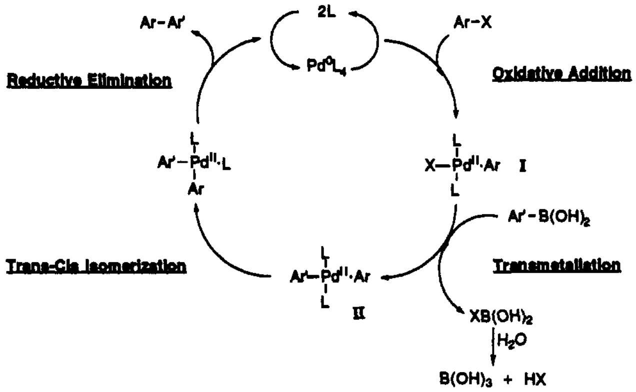

Figure 1.

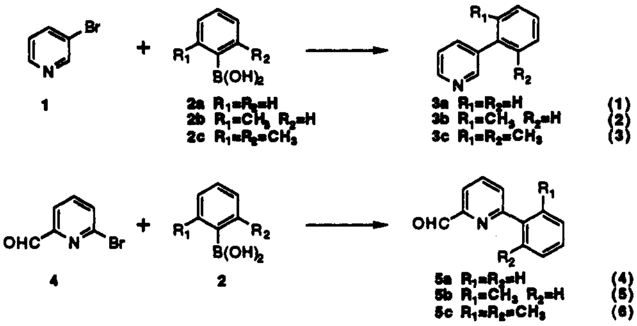

Figure 2. Palladium-catalyzed reactions of bromopyridines **1** and **4** with phenyboronic acids **2a–c**.

In the present study, pyridyl bromide **1** or **4** was reacted with each of three phenylboronic acids **2a–c** (Figure 2). Pyridyl halides were chosen to circumvent the problem, inherent to ESI-MS, that only preformed ionic species can be detected; protonation of the ring nitrogen permits the observation of normally uncharged species.[13] Three structurally similar arylboronic acids were selected, differing by the mass of only one methyl group.[14] Changes in the mass of the starting materials would then be reflected in mass shifts of the observed peaks. In each case, the coupling products were isolated and fully characterized.

Coupling reactions were initiated under normal conditions.[15] An aliquot of 40 μL of the organic phase of the reaction was removed and quenched in 0.5 mL of cold (−78 °C) methanol under a nitrogen atmosphere. Aliquots of the reaction samples were then injected into the mass spectrometer for analysis.[16] Reaction samples were warmed to room temperature immediately prior to injection.

As seen in Table 1, pyridylpalladium(II) complexes were observed in each of the experimental reactions in either of two forms, **I** $[(pyrH)Pd(PPh_3)_2Br]^+$ or **Ia** $[(pyr)Pd(PPh_3)_2]^+$ (probably a fragment from $[(pyr)Pd(PPh_3)_2Br]$).[17] In some cases,

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(13) Use of methanol/1% trifluoroacetic acid as the quench solvent did not appear to increase the relative intensity of protonated pyridine species.

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(15) To a stirred solution of 3.9×10^{-4} mol of aryl halide and 1.2×10^{-5} mol of $Pd(PPh_3)_4$ in 2 mL of toluene, under a nitrogen atmosphere, was added 1 mL of 2 M Na_2CO_3 and 4.8×10^{-4} mol of arylboronic acid dissolved in 0.5 mL of methanol. The reaction mixture was then placed in an oil bath at 80 °C. The reaction mixture was stirred vigorously throughout while being heated. Aliquots of the organic layer were taken at 45-min intervals until TLC indicated completion or no change in reaction.

(16) All ESI-MS experiments were performed on a Vestec Model 200 electrospray mass spectrometer. The general conditions for ESI-MS were as follows: needle voltage, 2.2 kV; ESI chamber temperature, 55 °C; repeller voltage, 200 V; lens temperature, 120 °C; block temperature, 250 °C. Syringe pump injection, flow rate = 4 μL/min. The 40-μL aliquots of reaction mixture were added to 0.5 mL of methanol and stored at low temperature (−78 °C) until analysis.

(17) None of the peaks that we report as reaction intermediates appear in ESI mass spectra of the starting materials. Aldehyde intermediates appeared as methanol hemiacetals. Hemiacetal formation by **4** in methanol solution was confirmed by ^{1}H NMR. Peak intensities, which vary from injection to injection, are listed in the supplementary material.

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Table 1. Electrospray Mass Spectral Data from Reactions 1–6 (Figure 2)^a

reaction						
1	2	3	4^f	5^{f,g}	6^f	assignment^h
788 (790)^{b,k}	789 (790)^l		849 (850)^{b,l}	849 (850)^l	849 (850)^l	**I**
708 (708)^c	708 (708)	709 (708)^l	768 (768)	769 (768)^l	768 (768)	**Ia**
788 (786)^{b,k}	800 (800)^d	814 (814)	(846)^b	860 (860)	874 (874)	**II**
(707)^c		735 (735)^e	709 (707)^k		735 (735)^e	**III**
578 (577)^{e,k}	578 (577)^{e,k}		579 (577)^e			**IV**
	1054^d		587^{d,e}		611	*j*
			1173^d			*j*

^{a} Reported peaks are highest intensity mass observed (calculated) in isotope envelope. Only peaks observed in two or more injections are listed. ^{b} **I** and **II** not resolved. ^{c} **Ia** and **III** not resolved. ^{d} Low relative intensity. ^{e} Peak also appears in spectrum of catalyst. ^{f} Aldehydes observed as methanol hemiacetals. ^{g} Only one injection. ^{h} Assignments: **I**, $[(PyrH)Pd(PPh_3)_2Br]^+$; **Ia**, $[(Pyr)Pd(PPh_3)_2]^+$; **II**, $[R_1R_2C_6H_3(PyrH)Pd(PPh_3)_2]^+$; **III**, $[R_1R_2C_6H_3Pd(PPh_3)_2]^+$; **IV**, $[Pd(PPh_3)_4]^{2+}$. ^{j} Unassigned. ^{k} Observed mass corresponds to calculated isotope of second-highest intensity. ^{l} Observed mass corresponds to average of the two most intense calculated isotopes.

species of similar molecular weight are not resolved due to the large number of naturally abundant palladium isotopes and the relatively low resolution (300) of the spectrometer. The less known diaryl Pd(II) species, $[(pyrH)(R_1R_2C_6H_3)Pd(PPh_3)_2]^+$ (**II**), was also consistently observed. Additionally, a species corresponding to $[(R_1R_2C_6H_3)Pd(PPh_3)_2]^+$ (**III**) was observed in reaction 4. The same peak was observed when the aryl halide was excluded from the reaction mixture and so may form by transmetalation with $Pd(PPh_3)_4^{2+}$ (**IV**). The peak corresponding to **IV** appeared in the spectrum of the catalyst alone, and its relative intensity increased with time.[18] The isotopic envelope for **IV** was half the size of those for **I**–**III**.

The peak assignments are consistent on both intraexperiment and interexperiment levels. The masses of the observed peaks correspond with predicted masses and isotopic distributions of the assigned species. When the experiments are compared in which the same aryl halide is used but the arylboronic acid is changed, we observed the same peak for **I** and/or **Ia**. A change in mass of 14 units was noted for the peak assigned to **II** each time a methyl group was added to the starting arylboronic acid,[19] corresponding to the differences in mass between phenyl, 2-methylphenyl, and 2,6-dimethylphenyl.

Although oxidative addition and transmetalation steps have long been thought to be involved in the catalytic cycle, our data confirm the presence of the proposed intermediates in the reaction milieu. The conventional notion that the transmetalation step is the slow step in the catalytic mechanism[8] would imply that intermediates formed from oxidative addition should predominate while all other intermediates are transient; yet we readily observe intermediate **II**, a post-transmetalation species.[20,21] Remarkably, the peaks corresponding to **II** were most easily observed with the most sterically hindered boronic acids. We did not observe the $[RPdL_2OH]$ or $[RPdL_2OCH_3]$ species proposed by Suzuki[7] or others.[22,23]

Our ESI-MS study does not provide quantitative or detailed structural information about the intermediates. However, we have been able to analyze the reaction mixture and observe mass spectra that correspond to the two key intermediates in the proposed mechanism for the Suzuki reaction. These results demonstrate that ESI-MS can be a valuable mechanistic tool when used in conjunction with other techniques.

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Supplementary Material Available: Observed and tabulated electrospray mass spectra, calculated isotopic distributions, and details regarding the synthesis and characterization of all new compounds (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(18) Some low-intensity, high-molecular-weight ($m/z > 1000$) peaks appear in the control and experimental reactions. These peaks cannot be assigned as reasonable mono- or dipalladium complexes. The masses also do not change consistently with systematic variation of the starting materials. We conclude that the species responsible for these peaks are probably not involved in the reaction.

(19) When the arylboronic acid was excluded from the reaction mixture, only the pyridylpalladium(II) **I** and **Ia** species were observed.

(20) In other exploratory studies, we have observed some cases in which only intermediates resulting from oxidative addition were observed. However, the absence of peaks corresponding to other intermediates does not prove that such intermediates are absent.

(21) Mass spectra of the reaction milieu from reaction 1 were not affected by the presence of compound **3c** (3.9×10^{-4} mol). Additionally, analysis of the reaction mixture containing **5c** but no pyridyl halide or arylboronic acid gave only base-line noise. We thank a referee for suggesting these experiments to rule out peaks resulting from N-coordinated coupled product/palladium complexes in the mass spectra.

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(23) There has been much speculation on the mechanism of the *trans*-to-*cis* isomerization of **II**. Our present results do not provide any information regarding this important question. For example, see: Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933–4941 and ref 11a.