On the amine-catalyzed Suzuki-Miyaura coupling using a catalysis-based fluorometric method

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Abstract. The Suzuki-Miyaura coupling is one of the most frequently used reactions in organic synthesis. Recent work by others suggested that an arylamine, prepared by palladium catalysis, could catalyze Suzuki-Miyaura coupling reactions without transition metals. Herein, we used a fluorometric quantification method for palladium previously developed in our laboratory to unambiguously conclude that there is a correlation between the palladium content in the arylamine and the rate of a Suzuki-Miyaura coupling. Also, our mass spectroscopic analysis of the arylamine revealed the presence of a palladium-phosphine complex. We discovered that the phosphine was detrimental to the palladium catalysis and that the arylamine played negligible role. This study demonstrates the utility of the fluorometric technology for catalysis research.

The palladium-catalyzed Suzuki-Miyaura coupling is one of the most frequently used reactions in organic synthesis.[1] However, due to the perceived toxicity and cost, there have been attempts to develop palladium-free Suzuki-Miyaura and related methods.[2-6] In several cases, trace palladium was present in the reagents and catalyzed the reactions.[4,7-12] In 2021, the Xu group reported an amine-catalyzed Suzuki-Miyaura-type coupling of aryl halides and arylboronic acids.[13] They prepared arylamine **1** by a palladium-catalyzed reaction between 1-bromo-2-methylbenzene and 2-methylbenzene 1,3-diamine in the presence of tricyclohexylphosphine (PCy_3) and purified the amine by standard column chromatography (Figure 1a).[13] In the presence of 5 mol% of this amine, Suzuki-Miyaura coupling products were formed in high yields (Figure 1b).[13] Their ICP-MS analysis showed 0.32 ppb palladium in the reaction mixture.[13] However, it was not clear to what "the solution" referred. We decided to investigate the reported coupling technology using our background in trace palladium detection methods.[8,14-22]

We prepared amine **1** according to the literature[13] (Figure 1a) and purified the product by four rounds of column chromatography followed by recrystallization to prepare five batches. These five batches are called **1-C1**, **1-C2**, **1-C3**, **1-C4**, and **1-RC**, reflecting the number of times the material was subjected to column chromatography or recrystallization.

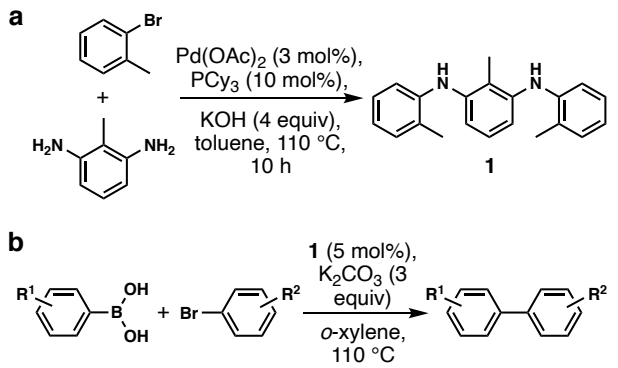

Figure 1. (a) Preparation of amine **1**.[13] (b) Suzuki-Miyaura coupling reported in the literature.[13] Cy, cyclohexyl.

Our laboratory has developed a method to colorimetrically or fluorometrically quantify trace palladium in complex matrices, including synthetic organic materials.[8,14-22] The technology proved to be sufficiently accurate in complex matrices when compared to other analytical techniques[16-18,21,22] and is used in the pharmaceutical industry.[19] The most recent variants of the technologies are the third[21] and fourth[22] generation methods. Although the fourth generation is more convenient, in this study we chose the third-generation method (Figure 2a) as the primary technique due to less likelihood of matrix interference.[21] With this method, the palladium concentrations in samples **1-C1**, **1-C2**, **1-C3**, **1-C4**, and **1-RC** were determined to be 65, 38, 12, 3.3, and 0.67 ppm in their solid state (Figure 2, Table 1, and Table 2).

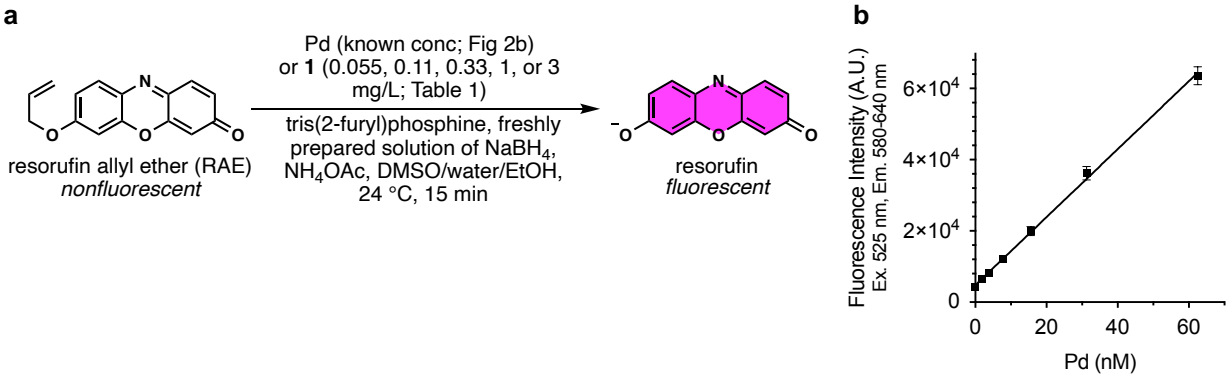

Figure 2, (a) Catalysis-based fluorometric method to quantify palladium. (b) Standard curve using the fluorometric method. Average ± standard deviation values are shown. y-axis = fluorescence intensity (A.U.) at 15 min – fluorescence intensity (A.U.) at 0 min. Conditions: 60 μM RAE, 180 μM tris(2-furyl)phosphine, 20 mM $NaBH_4$, 75 mM NaOH, 200 mM NH_4OAc, 8.7:17.0:74.3 v/v/v DMSO/water/EtOH, total volume 200 μL per well, 24 °C, 15 min. *n* = 3.

Table 1. Raw fluorescence data and calculated concentrations of palladium in five batches of amine **1** using the fluorescence method shown in Figure 2.

Conc of **1**	3.0 mg/mL		1.0 mg/mL		0.33 mg/mL		0.11 mg/mL		0.055 mg/mL	
	F.I.	Pd (nM)	F.I.	Pd (nM)	F.I.	Pd (nM)	F.I.	Pd (nM)	F.I.	Pd (nM)
1-C1	N/A	-	N/A	-	8.27	113	5.77	63	**3.83**	**34**
1-C2	N/A	-	N/A	-	7.11	88	**4.26**	**40**	3.33	27
1-C3	N/A	-	8.35	114	**4.05**	**37**	1.85	12	N/A	-
1-C4	8.17	110	**3.65**	**31**	1.57	9.1	0.849	3.8	N/A	-
1-RC	**2.62**	**19**	1.25	6.6	N/A	-	N/A	-	N/A	-

F.I.: Fluorescence intensity ($x10^4$)

Data shown in bold fit in the linear range of the standard curve.

N/A: Not applicable because the fluorescence values were outside of the linear range.

Table 2. Palladium concentrations after normalizing the amine concentration to 1.0 mg/mL and those in amine **1** in solid state using the data in bold in Table 1.

	Pd in 1.0 mg/mL of **1** (nM)	Pd in solid **1** (ppm)
1-C1	612	65
1-C2	360	38
1-C3	111	12
1-C4	31	3.3
1-RC	6.3	0.67

We performed the cross-coupling of $PhB(OH)_2$ and 4-bromo-1,1'-biphenyl with **1-C2**, **1-C3**, **1-C4**, and **1-RC** (**1-C1** was excluded due to fast kinetics) to reproduce the literature data (Figure 3a).[13] Because the Xu group used 5 mol% of amine **1** in most cases, we decided to use the same stoichiometry. Our preliminary study at 110 °C showed the reactions to be too fast to measure the initial rates. However, when the reactions were performed at 65 °C, the reaction rates were more tractable, yielding meaningful kinetic data. After 10, 20, 30, 45, 60, 75, and 120 min, we analyzed the reaction progress by ^1H NMR spectroscopy with Ph_3CH as an internal standard (Figure 3b). The product was undetectable when **1-RC** was used at 65 °C. When the reaction mixture with **1-RC** was heated to 110 °C as shown in the original work terphenyl was generated in quantitative yield after 24 h. We then plotted the concentrations of palladium in amine **1** in its solid state and the initial % conversion per minute (Figure 3c). From these data, we conclude that the reaction rates are linearly correlated with the palladium contents ($P < 0.0015$). During this study, two groups published their investigation on Xu's paper and concluded that trace palladium was responsible for the catalysis.[23,24]

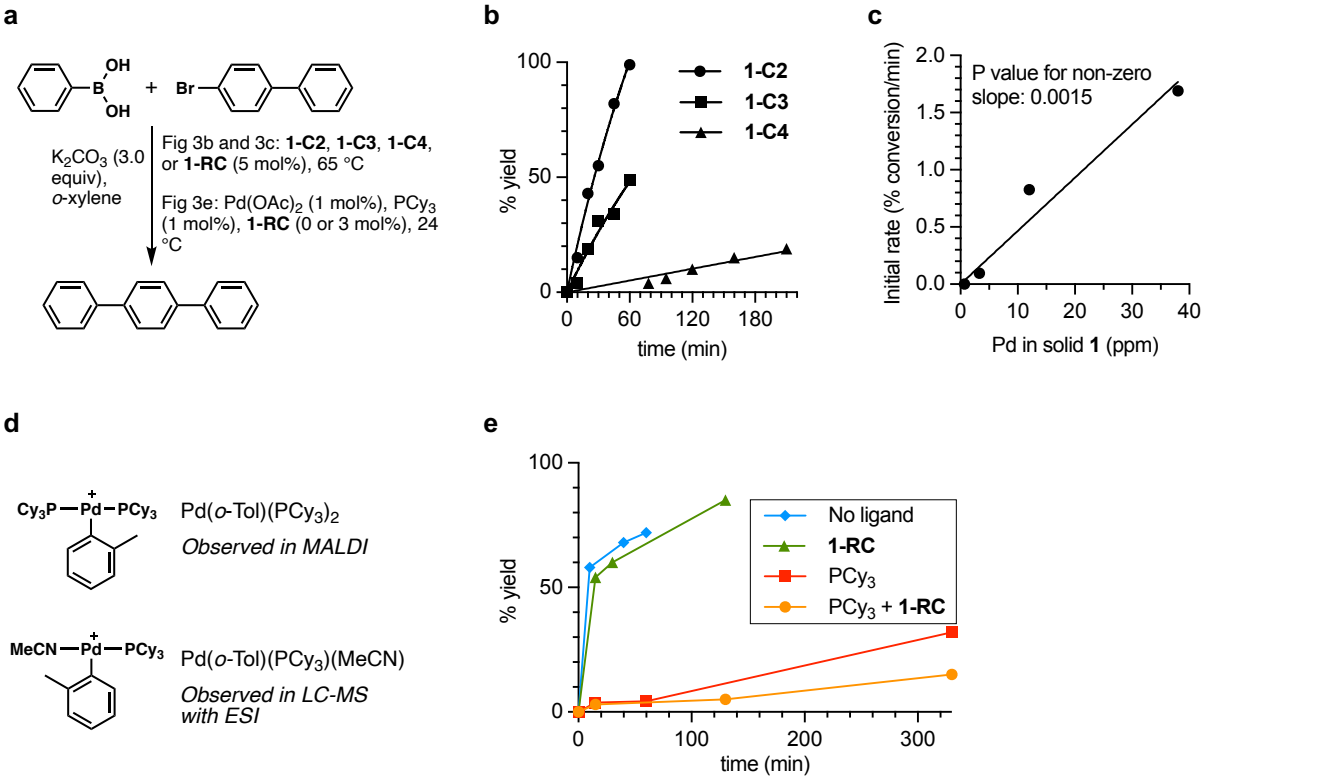

Figure 3. Suzuki-Miyaura coupling in the presence of amine **1**. (a) Model coupling system. (b) Reaction kinetics in the presence of **1**. (c) % conversion per minute versus palladium concentrations in solid **1**. (d) Structures of palladium complexes in amine **1** identified by MALDI and ESI with LC-MS using MeCN/water as eluent. (e) Suzuki-Miyaura coupling with palladium catalysis in the presence or absence of PCy_3 or **1-RC**.

The high-resolution mass spectroscopic data of **1-C2** showed the presence of palladium, as manifested by the characteristic isotope population for palladium (Spectrum S5, Supplementary Information). We propose that the palladium species in amine **1** may be Pd(*o*-Tol)$(PCy_3)_2$X (X = Cl or Br) (Figure 3d), which was also identified by the Wilkinson group.[24]

The relevance of amine **1** or PCy_3 to the catalysis was not studied by others.[23,24] As such, we reacted $PhB(OH)_2$ with 4-bromo-1,1'-biphenyl using 1 mol% $Pd(OAc)_2$ and 3 equiv of K_2CO_3 in the presence of the following reagent(s) *at room temperature*: (1) no additive, (2) 3 mol% **1-RC**, (4) 1 mol% PCy_3, or (5) 1 mol% PCy_3 and 3 mol% **1-RC**. Figure 3e shows that PCy_3 retarded the reaction and that amine **1** had negligible effects. These data may account for why elevated temperatures were needed when palladium-containing amine **1** was used for the coupling.[13,23,24]

In conclusion, this study shows that trace palladium in the purified batches of amine **1** was essential for Xu's results and that PCy_3 in the amine batches had detrimental effects. The amount of palladium in Xu's work with 5 mol% **1-C2** is at a homeopathic level[25]; specifically, the addition of 5 mol% of amine **1** with 65 ppm palladium means that approximately 9.3×10^{-4} mol% of palladium was present in the reaction mixture. In other words, the catalytic turnover number was at least 108 000, suggesting that the trace palladium species was

exceptionally reactive. Here, we compared palladium catalysis in the presence of amine **1**, PCy_3, and the combination of both, to find that PCy_3 had an inhibitory effect, which is reminiscent of Norrby's work with aryl iodides[26] and aryl chlorides.[27] Without amine **1** or PCy_3, we could lower the reaction temperature from 110 °C to 24 °C to carry out a ligand-free Suzuki-Miyaura coupling.[28] Despite many ligand-free examples, Suzuki-Miyaura couplings as part of drug production continue to use phosphine ligands.[29] The role of amine **1** with more complex substrates may warrant further study.

Author Contributions

K.K. conceived the study. J.K.V. prepared amine **1** and produced data shown in Figure 3. A.K.W. and E.I.J. produced data in Figure 2 and Table 1. All authors analyzed data.

Acknowledgements

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Abbreviations

Ac, acetyl; A.U., arbitrary unit; DMSO, dimethyl sulfoxide, Et, ethyl; g, gram; h, hour, Hz, hertz; M, molar; min, minutes; ppb, parts per billion; ppm, parts per million.

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Supplementary Information

On the amine-catalyzed Suzuki-Miyaura coupling using a catalysis-based fluorometric method

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General Information and Reagents.

Commercially available chemicals were purchased from Sigma-Aldrich or Alfa Aesar and used without further purification, unless otherwise indicated. Water used in this study was distilled. Reagent-grade DMSO was used without purification. Ethanol was USP-grade 200 proof. Trace-metal grade hydrochloric acid was purchased from Fisher. Resorufin allyl ether (RAE)[1] was stored at ambient temperature away from light. Tris(2-furyl)phosphine (TFP) was purchased from Fisher, and its solutions in DMSO were stabilized by hydroquinone and stored at ambient temperature in amber vials. Sodium borohydride pellets (1.00 g per pellet) were purchased from Fisher. A palladium standard solution was Atomic Absorption Spectroscopy (AAS) grade.

All the experiments were performed at ca. 24 °C unless stated otherwise. Fluorescence data were acquired using black round-bottomed 96-well plates and a Promega Biosystems Modulus II Microplate Reader (excitation 525 nm, emission 580–640 nm). GraphPad Prism 9.1.0 was used to generate graphs and perform statistical analyses.

Glassware was washed with 3% HCl and flamed-dried immediately prior use or oven-dried (80 °C, overnight). Solvents used for NMR spectroscopy were purchased from Cambridge Isotope Laboratories. $CDCl_3$ was stored over anhydrous K_2CO_3. All ^1H NMR spectra were recorded on Bruker AVANCE III 300, 400, and 500 MHz spectrometers and calibrated using either tetramethylsilane or residual solvent peaks as internal reference. NMR yields were determined by ^1H NMR spectra of the crude reaction mixtures using Ph_3CH as internal standard. Isolated yields refer to chromatographically purified materials, unless otherwise stated, and characterized by both NMR spectroscopy and high-resolution mass spectrometry (HRMS). The following abbreviations are used to indicate the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent, or combinations thereof. HRMS data were obtained on a GCT, Micromass UK Ltd and Q-Tof Ultima API, Micromass UK Ltd. Reactions were monitored using thin-layer chromatography (TLC) or ^1H NMR spectroscopic analysis of crude material. SilicaFlash P60 (230–400 mesh) was used for flash chromatography.

Preparation of amine 1

2-Methylbenzene 1,3-diamine (610 mg, 5.0 mmol), 1-bromo-2-methylbenzene (3.40 gg, 20.0 mmol, 4.0 equiv), $Pd(OAc)_2$ (34 mg, 0.15 mmol, 0.03 equiv), and tricyclohexylphosphine (140 mg, 0.50 mmol, 0.10 equiv), KOH (1.12 g, 20.0 mmol, 4.0 equiv) were placed in a transparent Schlenk tube equipped with a stirring bar. Toluene (25 mL) was added under a nitrogen atmosphere. The reaction mixture was stirred at 110 °C (oil bath temperature) for 10 h. The reaction mixture was cooled to room temperature, filtered through silica gel, and the filter cake was washed with EtOAc. The organic layers were combined and concentrated under vacuo. This procedure was repeated once, and the crude mixtures were combined. Glassware (column, flasks, and a bump trap for rotary evaporator) for the following column chromatography was washed with diluted HCl prior to use. The crude material was purified by flash column chromatography on silica gel (120 mL silica, hexanes/EtOAc = 30:1) to form **1-C1** (1.80 g, 63%). Approximately 1.55 g of this batch was purified by column chromatography on silica

gel (100 mL silica, hexanes/EtOAc = 30:1) to form **1-C2** (1.5 g). Approximately 1.25 g this batch was purified by column chromatography on silica gel (100 mL silica, hexanes/EtOAc = 30:1) to form **1-C3** (1.25 g). Lastly, approximately 950 mg of this batch was purified by column chromatography on silica gel (100 mL silica, hexanes/EtOAc = 30:1) to form **1-C4** (940 mg). A fraction of **1-C4** was recrystallized in EtOAc and hexanes to produce **1-RC** (600 mg).

Data for amine **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 7.4 Hz, 2H), 7.10(t, J = 7.8 Hz, 2H), 7.04 (t, J = 8.0 Hz, 2H), 6.87 (m, 4H), 6.72(d, J = 8.0 Hz, 2H), 2.28 (s, 6H), 2.12(s, 3H).). 2.28 (s, 6H), 2.12(s, 3H) HRMS (ESI) calcd for $C_{12}H_{23}N_2^+$[(M+H)$^+$] 303.1856, Found 303.1851. The spectroscopic data matched those in the literature.[2]

General Procedure for Kinetic Study

Method A (Figure 3b)

An internal standard stock solution was prepared by mixing Ph_3CH (1.5735 g, 6.4401 mmol) and biphenyl bromide (1.5000 g, 6.4350 mmol) in *o*-xylene (8.4 mL). Phenylboronic acid (118 mg, 0.96 mmol, 1.5 equiv), 2-methyl-N^1,N^3-di-*o*-tolylbenzene-1,3-diamine **1** (10.0 mg, 0.03 mmol, 0.05 equiv) and K_2CO_3 (267 mg, 1.93 mmol, 3.0 equiv) were placed in a sealed tube equipped with a stirring bar. The stock solution (1.2 mL) was added under an argon atmosphere. The reaction mixture was stirred at 65 ºC for 5 h. An aqueous workup with water/EtOAc on a small amount of reaction mixture was carried out in a vial. Organic layer was concentrated, dissolved in $CDCl_3$, and transferred to an NMR tube. The yield was determined by comparing the peaks at δ 5.55 (Ph_3CH) and δ 7.68 (s, 4H, terphenyl). The initial rates were calculated from the slopes of line with the zone of 0–20% conversion of terphenyl.

Method B (Figure 3e)

An internal standard stock solution was prepared by mixing triphenyl methane (4.4000 g, 18.008 mmol) and biphenyl bromide (4.2000 g, 18.018 mmol) in *o*-xylene (34 mL). The conversion of bromobiphenyl was obtained by comparing the peaks at δ 5.55 (Ph_3CH) and δ 7.54–7.57 (m, 4H, bromobiphenyl).

Procedure I: Phenylboronic acid (471 mg, 3.86 mmol, 1.5 equiv), K_2CO_3 (1.0680 g, 7.7279 mmol, 3.0 equiv), $Pd(OAc)_2$ (5.8 mg, 0.02 mmol, 1 mol%), PCy_3 (7.2 mg, 0.02 mmol, 1 mol%), and amine **1-RC** (23.3 mg, 0.08 mmol, 3 mol%) were placed in a 35-mL sealed tube equipped with a stirring bar. The stock solution (4.8 mL) was added under an argon atmosphere. The reaction mixture was stirred at room temperature for 5 h. An aqueous workup with water/EtOAc on a small amount of reaction mixture was carried out in a vial. Organic layer was concentrated, dissolved in $CDCl_3$, and transferred to an NMR tube.

Procedure II: Phenylboronic acid (471 mg, 3.86 mmol, 1.5 equiv), K_2CO_3 (1.0680 g, 7.7279 mmol, 3.0 equiv.), $Pd(OAc)_2$ (5.8 mg, 0.02 mmol, 1 mol%), and amine **1-RC** (23.3 mg, 0.08 mmol, 3 mol%) were placed in a 35-mL sealed tube equipped with a stirring bar. The stock solution (4.8 mL) was added under an argon atmosphere. The reaction mixture was stirred at room temperature for 5 h. An aqueous workup with water/EtOAc

on a small amount of reaction mixture was carried out in a vial. Organic layer was concentrated, dissolved in $CDCl_3$, and transferred to an NMR tube.

Procedure III: Phenylboronic acid (471 mg, 3.86 mmol, 1.5 equiv), K_2CO_3 (1.0680 g, 7.7279 mmol, 3.0 equiv), $Pd(OAc)_2$ (5.8 mg, 0.02 mmol, 1 mol%) and PCy_3 (7.2 mg, 0.02 mmol, 1 mol%) were placed in a 35-mL sealed tube equipped with a stirring bar. The stock solution (4.8 mL) was added under an argon atmosphere. The reaction mixture was stirred at room temperature for 5 h. An aqueous workup with water/EtOAc on a small amount of reaction mixture was carried out in a vial. Organic layer was concentrated, dissolved in $CDCl_3$, and transferred to an NMR tube.

Procedure IV: Phenylboronic acid (471 mg, 3.86 mmol, 1.5 equiv), K_2CO_3 (1.0680 g, 7.7279 mmol, 3.0 equiv.), and $Pd(OAc)_2$ (5.8 mg, 0.02 mmol, 1 mol%) were placed in a 35-mL sealed tube equipped with a stirring bar. The stock solution (4.8 mL) was added under an argon atmosphere. The reaction mixture was stirred at room temperature for 5 h. An aqueous workup with water/EtOAc on a small amount of reaction mixture was carried out in a vial. Organic layer was concentrated, dissolved in $CDCl_3$, and transferred to an NMR tube.

Procedure for Figure 2 (Quantification of palladium)

Preparation of 85.7 μM RAE/286 mM NH_4OAc in 10.7:89.3 v/v DMSO/EtOH: (1) RAE (25.3 mg) was dissolved in DMSO (20.00 mL) in an amber vial to prepare 5.0 mM RAE in DMSO. (2) An aliquot of this solution (8.0 mL) was diluted with EtOH (42.0 mL) in an amber bottle to prepare 800 μM RAE in 4:21 v/v DMSO/EtOH solution. (3) The 800 μM RAE solution in DMSO (32.14 mL) was mixed with 500 mM NH_4OAc (171.6 mL) and EtOH (96.26 mL). The resulting solutions were stored at -20 °C.

Preparation of 15.0 mM TFP in DMSO: Butylated hydroxytoluene (BHT, 12.5 mg) was dissolved in DMSO (50 mL) in an amber bottle to prepare 250 ppm BHT in DMSO. The BHT solution in DMSO (6.667 mL) was used to dissolve TFP (23.2 mg, 100 μmol) in an amber bottle to prepare 15.0 mM TFP in DMSO. The resulting solution can be stored at room temperature for at least 6 months.

Preparation of 2.0 mM Pd solution in trace metal HCl: (1) 1000 ppm Pd in 10% HCl (240 μL) was diluted with 0.7M trace metal HCl in water (896 μL) to prepare 2.0 mM Pd solution, which can be stored for at least 3 months.

Preparation of Pd samples: (1) 0.50 M HCl in 1:4 v/v DMSO/water was prepared (solution **A**). (2) A solution of 2.0 mM Pd in 3% HCl was 10-fold serially diluted twice (200 μL) with solution **A** (1.800 μL) to prepare 200 μM and 20 μM Pd. (3) The 20 μM Pd (1000 μL) was 2-fold serially diluted ten times with solution **A** (1000 μL) to prepare 19.5, 39, 78, 156, 313, 625, 1250, 2500, 5000, 10000, 20000 nM Pd in solution **A**. Solution **A** was used as 0 nM Pd. Pd solutions were discarded after 12 h.

Preparation of 2.67 M $NaBH_4$ and 10 M NaOH: One $NaBH_4$ pellet (1.00 g, 26.4 mmol) was dissolved in cold aqueous 10 M NaOH (9.91 mL) to prepare 2.67 M $NaBH_4$ and 10 M NaOH in water. The solution was kept

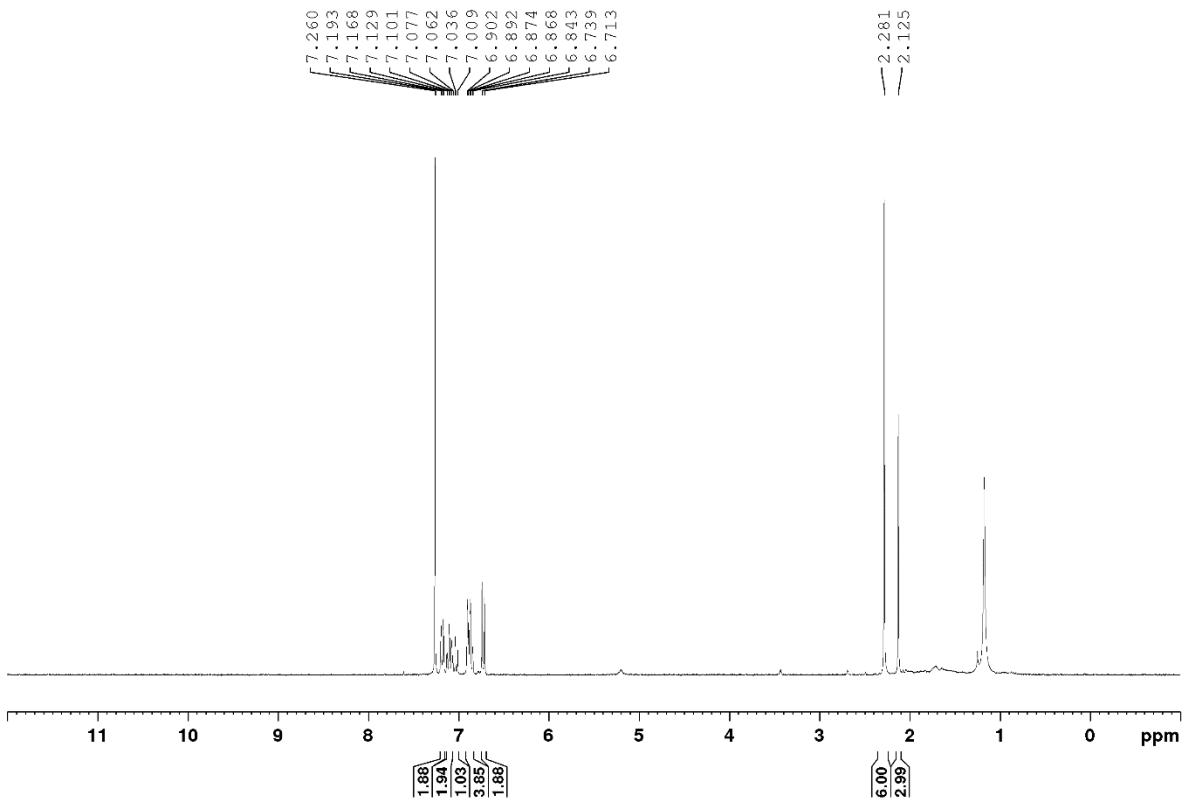
on ice for up to 8 h (this solution should be prepared within 8 h prior to use. CAUTION: Do not store the solution in a refrigerator due to the gradual evolution of hydrogen gas.

Preparation of amine samples for palladium analysis: (1) Amine **1-C1**, **1-C2**, **1-C3**, **1-C4**, and **1-RC** (5.00 mg each) were weighed using a precise analytical balance into clear glass vials. (2) The samples were dissolved in DMSO to prepare 5.0 mg/mL solutions. (3) These solutions (600 μL) were diluted with 625 mM HCl (400 μL) to prepare 3.0 mg/mL solutions of **1-C1**, **1-C2**, **1-C3**, **1-C4**, and **1-RC**. (4) Three rounds of 3-fold serial dilutions were performed with 300 μL of sample and 600 μL of solution **A** to prepare 1, 0.33, and 0.11 mg/mL solutions of **1-C1**, **1-C2**, **1-C3**, **1-C4**, and **1-RC**. (5) With **1-C1** and **1-C2** samples, a 2-fold dilution of 0.11 mg/mL sample (300 μL) with solution **A** (300 μL) was performed to prepare 0.055 mg/mL solutions of **1-C1** and **1-C2**.

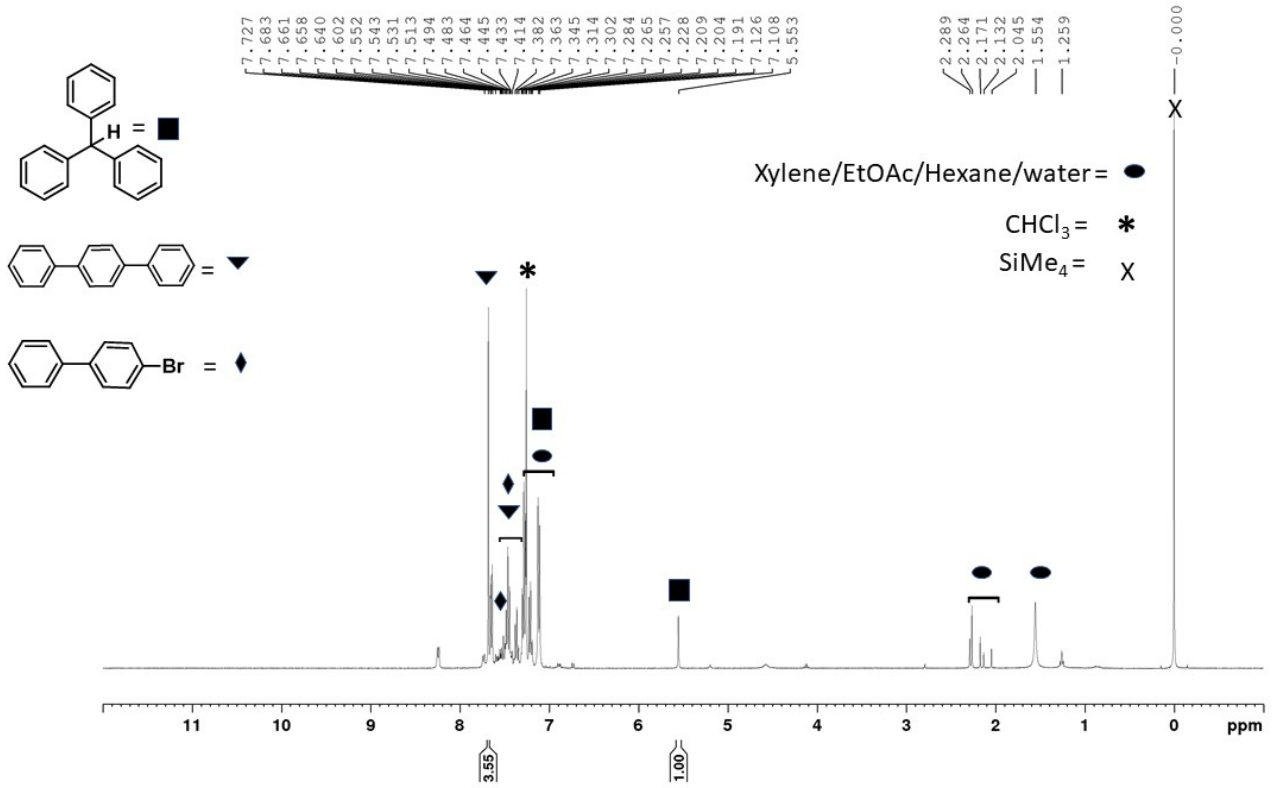
Preparation of 900 μM TFP/100 mM $NaBH_4$/375 mM NaOH in 6:44:50 v/v/v DMSO/EtOH/water: (1) The 2.67 M $NaBH_4$ and 10 M NaOH in water (1.80 mL) was diluted with water (10.20 mL) in a 15 mL conical centrifuge tube to prepare 400 mM $NaBH_4$ and 1.5 M NaOH in water. (2) This solution (3.00 mL), cold EtOH (5.28 mL), 15.0 mM TFP in DMSO (720 μL), and water (3.00 mL) were mixed in a reservoir to prepare 900 μM TFP/100 mM $NaBH_4$/375 mM NaOH in 6:44:50 v/v DMSO/EtOH/water.

Assay: Final conditions: 180 μM TFP, 60 μM RAE, 20 mM $NaBH_4$, 75 mM NaOH, 200 mM NH_4OAc, 8.7:17.0:74.3 v/v DMSO/water/EtOH, total volume 200 μL per well, 24 °C, n = 3. (1) A solution of 85.7 μM RAE/286 mM NH_4OAc in 10.7:89.3 v/v DMSO/EtOH (140 μL) was transferred to wells in a black 96-well plate. (2) A solution of 0, 19.6, 39.1, 78.1, 156, 313, 625, 1250, 2500, or 5000 nM Pd (20 μL) was transferred to wells for correlation curve. (3) Samples **1-C1**, **1-C2**, **1-C3**, **1-C4**, and **1-RC** at concentrations 3.0–0.055 mg/mL (20 μL) were transferred to wells. (4) A solution of 900 μM TFP/100 mM $NaBH_4$/375 mM NaOH in 6:44:50 v/v/v DMSO/EtOH/water solution (40 μL) was transferred to wells. (4) Fluorescence measured every 15 min for 60 min. (5) $F_{15min} - F_{0min}$ values were calculated.

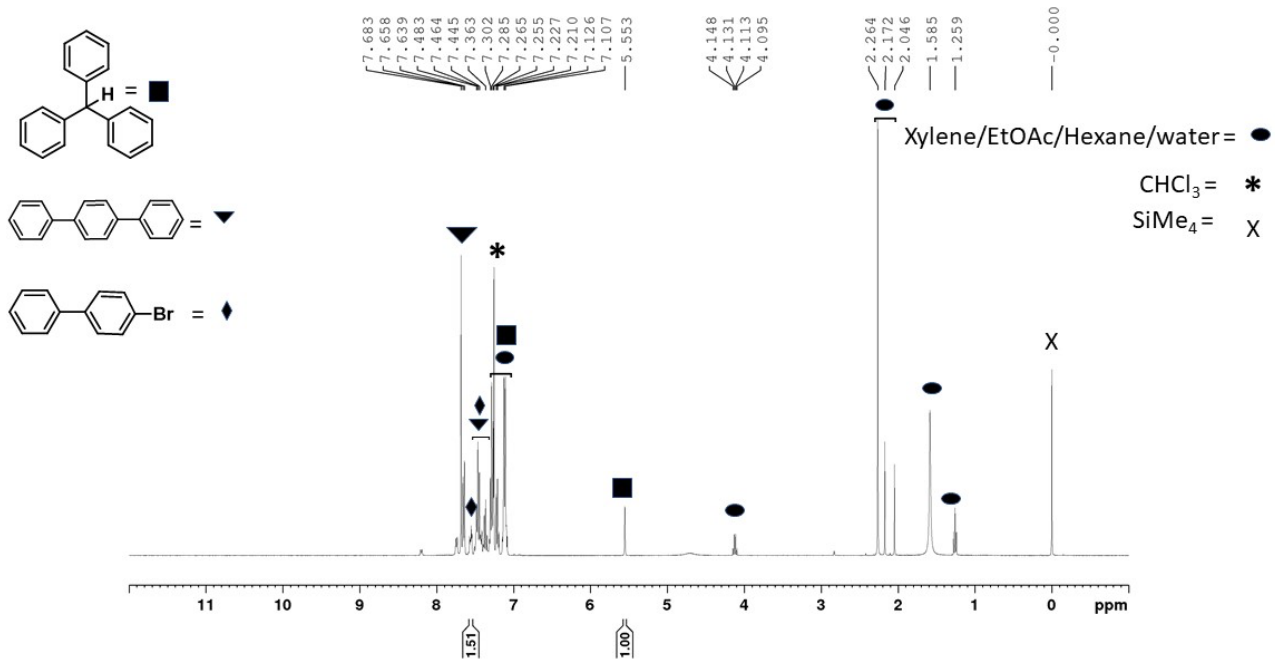
Spectrum S1. ^{1}H NMR spectrum of amine **1** (300 MHz, $CDCl_3$, 298 K)



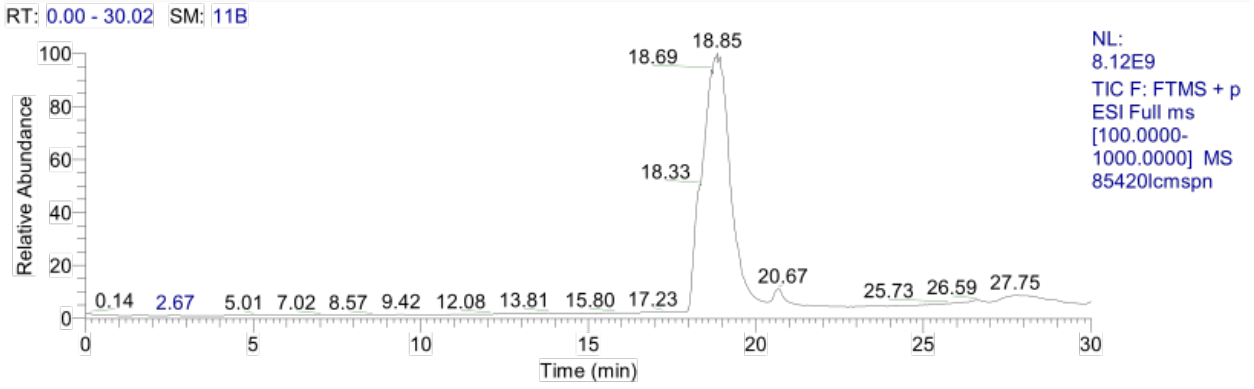
Spectrum S2. Representative ^{1}H NMR spectrum of crude mixture for kinetic experiments in Figure 3b (400 MHz, $CDCl_3$, 298 K)

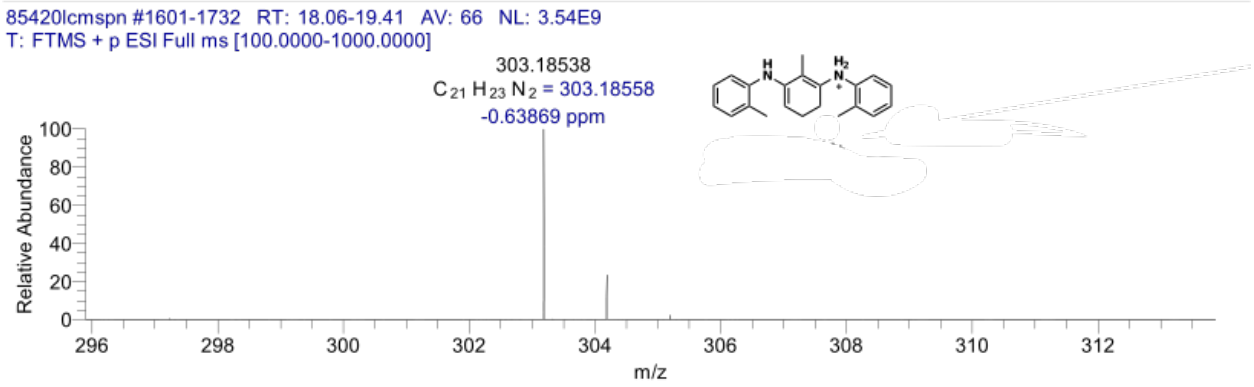


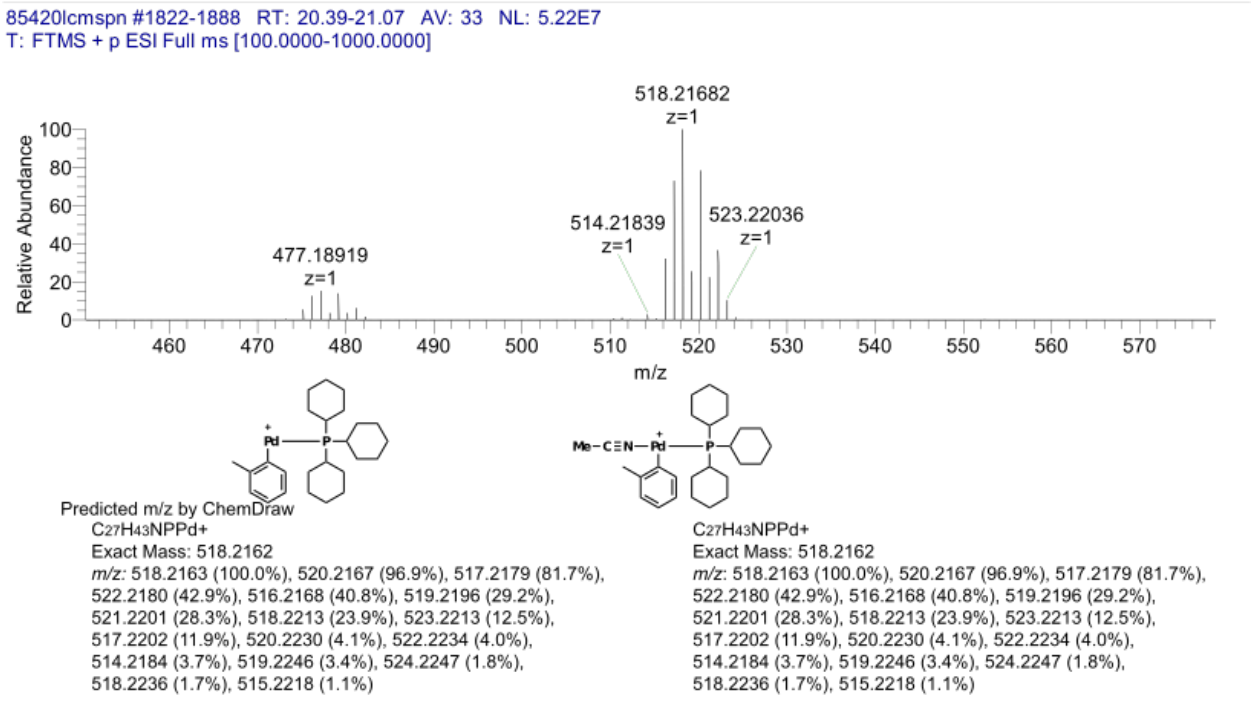
Spectrum S3. Representative ^{1}H NMR spectrum of crude mixture for kinetic experiments in Figure 3e (400 MHz, $CDCl_3$, 298 K)



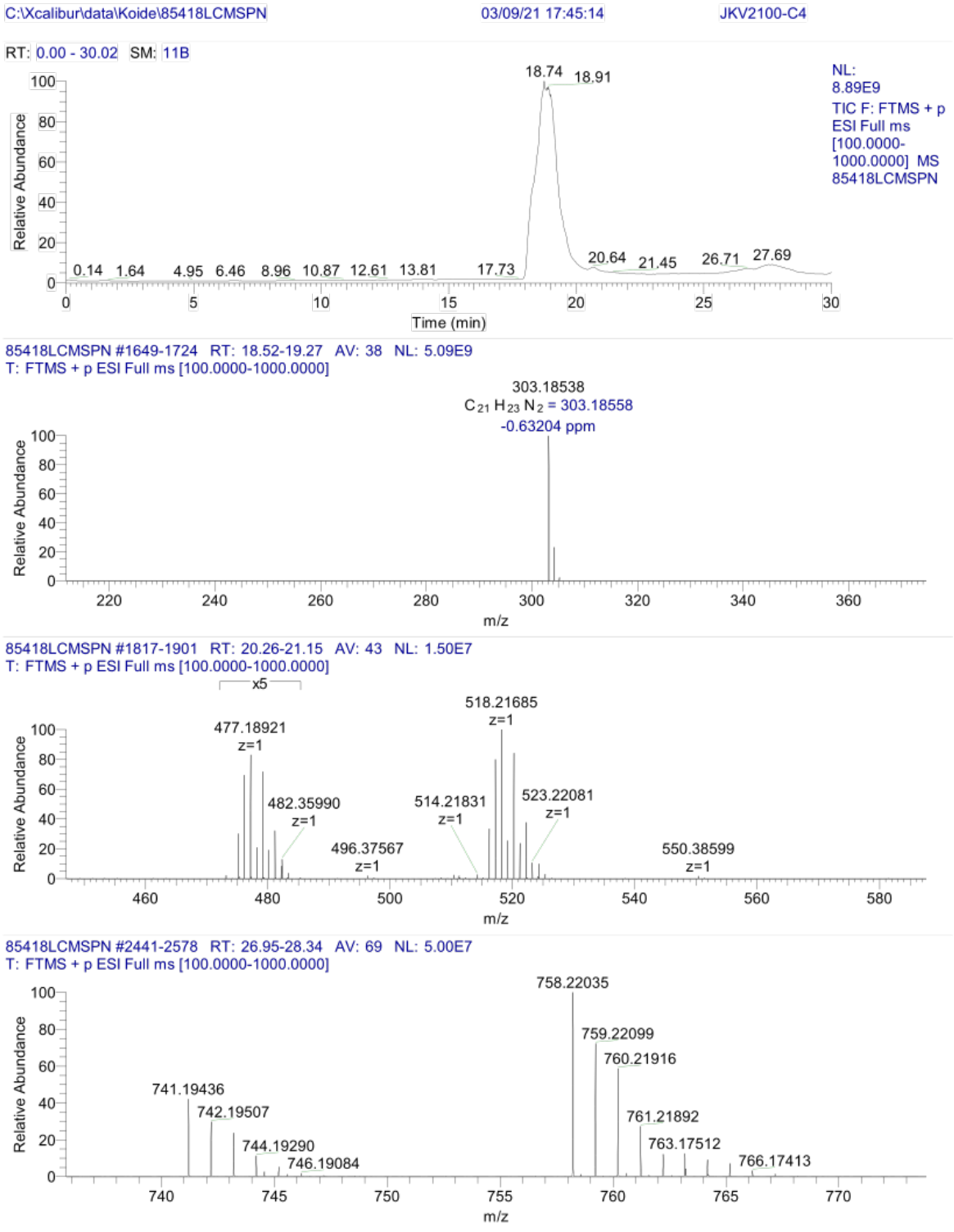
Spectrum S4. LCMS Spectrum of **1-C3** for Figure 3d



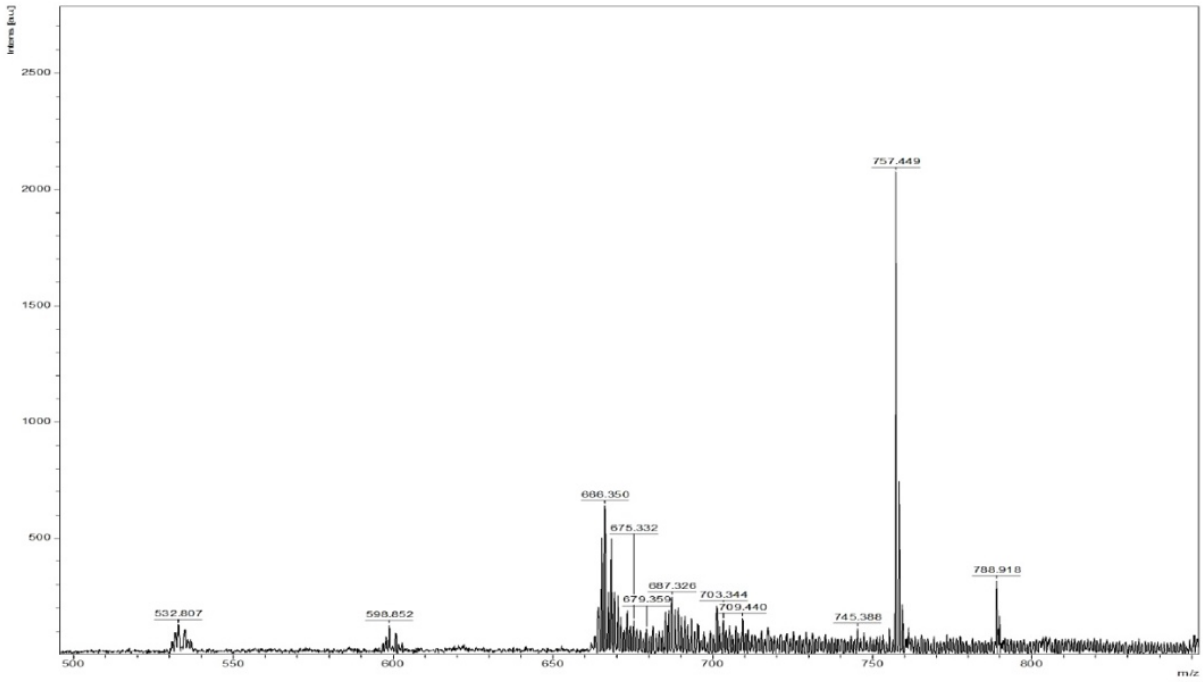




Spectrum S5. LC-MS Spectrum of **1-C4** (ESI)



Spectrum S6. MALDI-TOF mass spectra of **1-C3** for Figure 3d.



m/z	S/N	Quality Fac.	Res.	Intens.	Area
530.824	4		2143	58.0	20.0
531.823	7		1087	96.0	54.7
532.807	9		1110	129	74.7
534.833	8		1164	108	64.9
535.781	5		992	63.4	45.1
536.771	5		1234	64.9	36.9
597.845	5		2756	77.0	24.4
598.852	8		2566	127	38.8
600.849	6		2299	92.9	27.8
664.336	9		2959	204	49.1
665.349	23		3046	502	103
666.350	29		2983	641	125
667.345	12		3043	269	58.8
668.350	22		2943	498	98.8
669.343	12		2960	268	60.9
670.351	11		3073	255	52.2
671.342	7		2636	162	49.1
672.329	5		2905	104	34.0
673.331	8		3128	190	45.3
674.317	5		2849	125	38.9
675.332	6		2710	147	43.4
676.338	5		2655	113	37.3
677.387	5		1787	106	42.4
679.359	5		1976	112	38.2
681.400	5		2349	123	42.0
683.353	4		2765	102	34.5
684.332	4		2630	103	31.0
685.360	8		2829	185	51.2
686.339	8		2916	191	50.1
687.326	10		3119	250	55.8
688.322	8		3130	196	45.9
689.337	8		3168	201	48.1
690.338	7		2757	160	45.1
691.338	7		2605	165	55.9
692.356	5		2883	129	37.1
693.434	7		2243	157	51.2
694.462	4		1836	101	38.7
695.472	6		2026	134	51.3
697.385	4		1922	99.1	40.2
699.369	4		2617	103	31.1
701.371	9		3017	212	51.9
702.363	5		3043	122	36.4
703.344	6		2760	149	44.3
704.332	4		3058	104	28.4
705.353	5		1740	126	49.8
707.383	5		2414	123	39.4
709.440	6		1975	156	53.3
711.303	4		1939	109	40.2
717.367	5		2607	117	37.4

Table S1.

Pd (nM)	Fluorescence Intensity (A.U.)		
500	137625	181234	236089
250	115285	128154	143991
125	68062	88598	99949
62.5	63175	61282	66275
31.3	34376	38128	36154
15.6	20152	18639	21244
7.81	12044	11932	12267
3.91	8033	8115	8565
1.96	6322	6406	6763
0	4545	3563	4758

1-C1

1-C1 (mg/mL)	Fluorescence Intensity (A.U.)		
3.0	96 081	102 732	96 756
1.0	95 261	98 156	92 501
0.33	83 496	81 196	83 420
0.11	57 035	55 663	60 478
0.055	34 461	39 040	41 486

1-C2

1-C2 (mg/mL)	Fluorescence Intensity (A.U.)		
3.0	103 797	114 914	120 581
1.0	104 030	94 598	94 251
0.33	70 403	71 994	70 787
0.11	39 130	45 948	42 803
0.055	28 556	36 423	34 881

1-C3

1-C3 (mg/mL)	Fluorescence Intensity (A.U.)		
3.0	129 039	123 704	114 286
1.0	84 430	83 868	82 080
0.33	39 794	39 951	41 639
0.11	18 767	18 579	18 224

1-C4

1-C4 (mg/mL)	Fluorescence Intensity (A.U.)		
3.0	84 538	81 162	79 483
1.0	38 333	35 491	35 686
0.33	15 086	15 371	16 532
0.11	8 642	8 172	8 667

1-RC

1-RC (mg/mL)	Fluorescence Intensity (A.U.)		
3.0	23 601	29 321	25 747
1.0	13 427	11 842	12 285
0.33	7 063	6 731	6 581
0.11	5 243	4 806	4 627

Cited References

1 Koide, K. *et al.* A competitive and reversible deactivation approach to catalysis-based quantitative assays. *Nat. Commun.* **7**, 10691 (2016).

2 Xu, L. *et al.* The amine-catalysed Suzuki–Miyaura-type coupling of aryl halides and arylboronic acids. *Nat. Catal.* **4**, 71-78 (2021).