

Kinetics and mechanism of heterogeneous palladium-catalyzed coupling reactions of chloroaryls in water

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Coupling reactions of substituted chlorobenzenes to biphenyls catalyzed by palladium on carbon are performed in water using sodium hydroxide and sodium formate in the presence of a surface active agent. Thus, chlorobenzene, *p*-chloro-*o*-xylene, *p*-chloro-1,1,1-trifluorotoluene, *p*-chloroanisole, and *p*-chlorotoluene are coupled under moderate conditions to the respective biaryls. A competing reduction process occurs (*e.g.* chlorobenzene is reduced to benzene), which can be minimized by altering conditions. The relationship of product selectivity to reaction temperature, formate concentration, base concentration, and surfactant type is examined. The roles of formate, Pd catalyst, and surfactant are discussed. It is proposed that the reduction is dependent on the participation of palladium hydride [Pd²⁺(H⁻)₂], while the coupling occurs *via* single electron-transfer from Pd⁰ to the substrate, with subsequent decomposition of the chloroaryl radical anions to obtain aryl radicals and chloride anions. This mechanism is supported by experiments with stoichiometric and sub-stoichiometric amounts of palladium which indicate that selective coupling can occur also in the absence of hydrogen (providing that reduced palladium Pd⁰, is present in sufficient amount), and by kinetic investigations which indicate that the coupling is actually a first-order reaction, for which the rate-determining step may be the dissociation of the chloroaryl radical anion.

Introduction

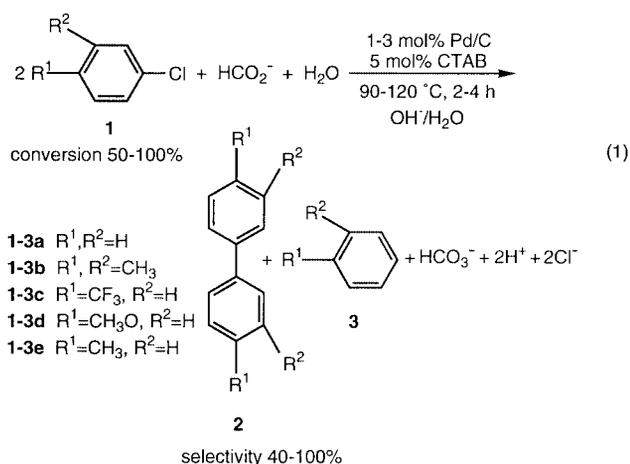
Preparation of biaryl compounds is of interest to many organic chemists and relates to numerous applications, the biaryl moiety being a key building block of many agrochemicals, pharmaceuticals, and natural products.¹ For example, substituted biphenyls are the backbone of new angiotensin-blocking drugs called sartans for control of high blood pressure.² To meet market needs several synthetic approaches towards biphenyl coupling have been developed, from the classic general Ullmann³ and Suzuki⁴ reactions to custom-tailored catalytic transformations aimed at specific molecules.

Various Pd-catalyzed biaryl syntheses are described in the literature as alternatives to the stoichiometric Ullmann reaction with copper. In several cases, stoichiometric amounts of amines were used as hydrogen donors to regenerate the Pd catalyst.⁵ Yields are generally moderate to good. The homogeneous Buchwald catalyst allows high-yield Suzuki coupling of arylborons and aryl chlorides to obtain biphenyls at room temperature.² Recently, Hassan *et al.* demonstrated⁶ that homogeneous palladium acetate can catalyze the homo-coupling of aryl and heteroaryl halides, but the homogeneous catalyst could not be recycled.

It is also possible to use a heterogeneous mixture of palladium on carbon as the catalyst together with a sodium formate solution as the terminal reductant. This approach is especially appealing as an industrial solution, as the potential of catalyst recycling seems high. The utility of this simple system was recognized over twenty years ago.⁷ In this paper we present findings that pertain to the various catalytic coupling and reduction transformations which occur in this palladium/formate/aryl system, and discuss possible mechanisms for the reactions involved.

Results

In a typical reaction [eqn. (1)], two molar equivalents of



chloroaryl were stirred together with a slight excess of sodium formate, in the presence of sodium hydroxide, a phase-transfer catalyst (PTC) such as cetyltrimethylammonium bromide (CTAB), a catalytic amount of Pd/C, and water. Biaryl was found to be the major product, together with some hydro/dehalogenation product. No other products were observed.

Moderate to good yields of the coupling products were obtained using various substrates, as shown in Table 1. The palladium catalyst was easily recycled by simple filtration followed by a short reflux in MeOH. In three such cycles no appreciable reduction in catalyst activity was observed. Chlorobenzene **1a** was chosen as a model substrate for the kinetic and process parameter studies.

Formate concentration was found to influence both substrate conversion and product selectivity (Fig. 1). Optimal yields of the coupling product were obtained when [HCO₂⁻] was between 3 and 5 M.

Substrate conversion *and* selectivity towards the coupling product also increased (from 46% conversion and 38% selectivity to 92–3% conversion and 87% selectivity) with the addition of hydroxide. This effect reached a plateau at an NaOH concentration of 25% w/v (2.8 equivalents relative to substrate).

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Table 1 Palladium-catalyzed coupling and reduction of chloroaryls

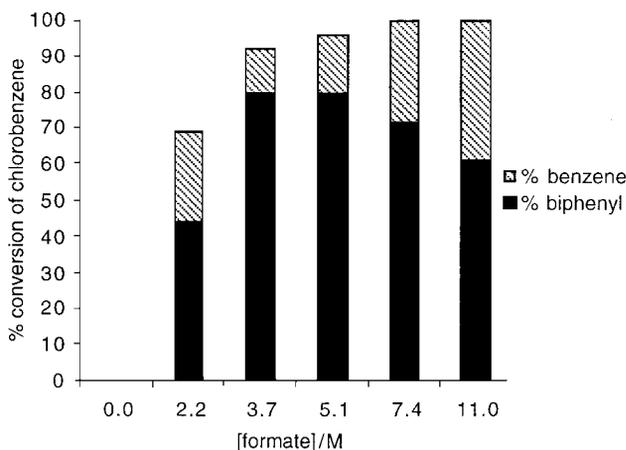
Entry	Substrate	Time/h ^a	Coupling (%) ^{b,c}	Reduction (%) ^b
1	1a	1 1/2	87 (83)	13
2	1a^d	1 1/4	88 (83)	12
3	1b	4	25 (20)	75
4	1c	1 1/4	82 (75)	18
5	1d	5	21 (20)	79
6	1e	2	67 (60)	33

Reaction conditions: 80–100 mmol substrate, 150 mmol NaHCO₂, 250 mmol NaOH, 0.7 mmol of 10% Pd/C (1 mol% of Pd relative to substrate), 3–5 mol% CTAB, 40 ml H₂O, 110 °C, autoclave. ^a Time required for 100% substrate conversion. ^b Yield based on GC area, corrected by the presence of an internal standard. ^c The numbers in parentheses represent isolated yields. ^d KHCO₂ was used instead of NaHCO₂.

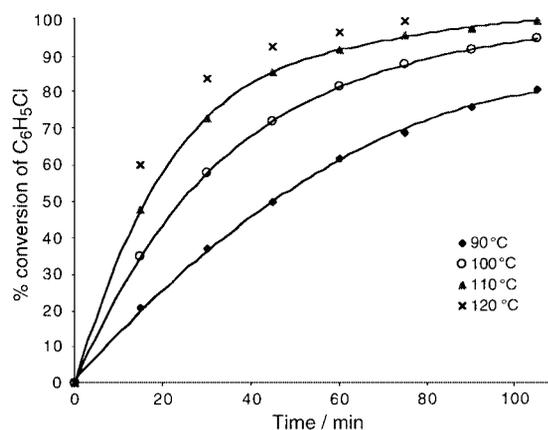
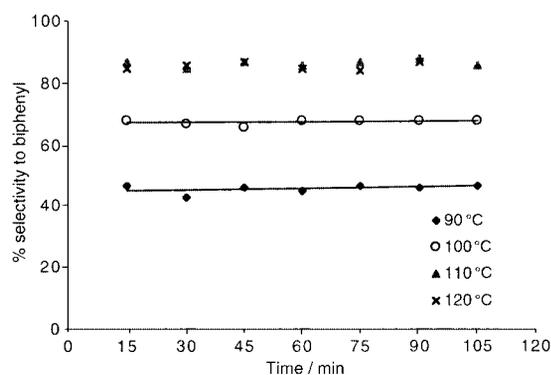
Table 2 Effects of different PTCs on **1a** conversion and product selectivity

Entry	PTC type	Conversion of C ₆ H ₅ Cl (%)	Selectivity to biphenyl (%)
1	None	60	29
2	(Me) ₃ (C ₁₆ H ₃₃)N ⁺ Br ⁻	93	87
3	(<i>n</i> -Bu) ₄ N ⁺ Br ⁻	93	71
4	(<i>n</i> -Bu) ₄ N ⁺ F ⁻	92	41
5	(<i>n</i> -Bu) ₄ N ⁺ I ⁻	79	51
6	(<i>n</i> -Bu) ₄ N ⁺ (OAc) ⁻	86	63
7	(<i>n</i> -Bu) ₄ P ⁺ Br ⁻	64	53
8	(Et) ₃ (Bz)N ⁺ Cl ⁻	85	31
9	(<i>n</i> -Hex) ₄ N ⁺ I ⁻	79	51
10	(Me) ₃ (C ₆ H ₅)P ⁺ Br ⁻	42	29
11	[(Et) ₃ Si(CH ₂) ₃](Me) ₃ N ⁺ Br ⁻	48	30
12	PEG-400	62	73

Reaction conditions: 88 mmol C₆H₅Cl, 150 mmol NaHCO₂, 250 mmol NaOH, 0.7 mmol of 10% Pd/C (1 mol% of Pd relative to C₆H₅Cl), 40 ml H₂O, 110 °C, autoclave, 1 h.

**Fig. 1** Effect of formate concentration on **1a** conversion and product selectivity. Reaction conditions: 88 mmol C₆H₅Cl, 250 mmol NaOH, 1 mol% Pd/C, 9 mol% CTAB, 40 ml H₂O.

Performing the reaction in the presence of catalytic amounts of various PTCs gave inconclusive results. While addition of a PTC always improved the substrate conversion, the selectivity towards biphenyl ranged from 87% using CTAB to 31% using benzyltriethylammonium chloride (Table 2). This is in accordance with the results reported by Bamfield and Quan, who found that different phase-transfer agents and surfactants were needed to maximize yield, depending on the substrate employed.⁷ The nonionic surfactant polyethylene glycol 400 (PEG-400) also improved substrate conversion and product selectivity, and might suit applications on a larger scale as it is

**Fig. 2** **1a** conversion profiles at different temperatures. Reaction conditions: 88 mmol C₆H₅Cl, 250 mmol NaOH, 150 mmol NaHCO₂, 1 mol% Pd/C, 9 mol% CTAB, 40 ml H₂O.**Fig. 3** Selectivity towards coupling profiles at different temperatures. Reaction conditions: 88 mmol C₆H₅Cl, 250 mmol NaOH, 15 mmol NaHCO₂, 1 mol% Pd/C, 9 mol% CTAB, 40 ml H₂O.

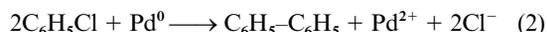
cheaper, more stable, and more easily separated than the quaternary ammonium salts.

Performing the reaction at higher temperatures led to a faster reaction rate with respect to substrate conversion, as expected. However, the selectivity towards the coupling product increased with temperature until a plateau was reached at 110 °C (*cf.* conversion and selectivity profiles in Figs. 2 and 3). Note too that product selectivity remains roughly constant throughout the reaction.

Remarkably, the kinetics of this coupling reaction were found to fit a first-order profile (*e.g.* $k_{\text{obs}} = 29 \times 10^{-2} \text{ min}^{-1}$, with $r^2 = 0.996$ for 9 observations). The calculated Arrhenius energy of activation was $E_a = 50 \text{ kJ mol}^{-1}$ (12.5 kcal mol⁻¹, $r^2 = 0.983$ for four measurements at 90, 100, 110, and 120 °C), a typical value for a chemically controlled rate-determining step.

When reactions were performed using variable catalyst loadings it was found that increasing the amount of palladium catalyst also increases the selectivity towards the coupling product. Thus, selectivities of 38, 60, 83, and 85% for biphenyl were observed when 0.25, 0.5, 0.9, and 1 mol% of palladium (relative to substrate) were employed. The conversion and selectivity profiles were similar to those obtained with increased temperatures, *i.e.* a constant product ratio was reached at a low substrate conversion and maintained.

Evidently, the coupling and the reduction reactions are competing transformations in this system. However, product selectivity can be shifted towards exclusive coupling owing to the fact that the reduction reaction requires a hydrogen atom, while the coupling requires only electrons that can be provided by the reduced palladium catalyst. This was evidenced from a reaction between **1a** and *stoichiometric* palladium [eqn. (2)], in which a



quantitative yield for **2a** was obtained. Moreover, similar results were obtained when a semi-stoichiometric setup was employed. Thus, when the reaction was performed using semi-stoichiometric amounts of palladium (20 mol% Pd), a 20% yield of biphenyl was measured after 1 h. At this time, 20 mol% of formate were added, and a further 20% yield of biphenyl was recorded. Adding a further batch of formate resulted in 100% conversion of the chlorobenzene and a quantitative yield of biphenyl was obtained. Biphenyl was also formed as the sole product when a similar semi-stoichiometric reaction was carried out in the absence of base, but the reaction rate was ten times slower.

Discussion

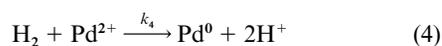
Competition between reduction and coupling reactions

When a stoichiometric amount of palladium is employed (in the absence of formate), quantitative conversion of chlorobenzene to biphenyl is observed. However, when a catalytic amount of palladium is used together with formate as the terminal reductant, some reduction of chlorobenzene to benzene is also observed. We assume that this reduction is caused by the presence of dihydrogen.

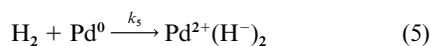
We have previously shown that formate reacts with water in the presence of a palladium catalyst to give bicarbonate and dihydrogen [eqn. (3)]. In fact, the combination of formate and



water can be regarded as a source of hydrogen in the presence of palladium. Dihydrogen can reduce Pd^{2+} to Pd^0 [eqn. (4)], and



can also dissociate on the surface of Pd^0 [eqn. (5)]. However, the



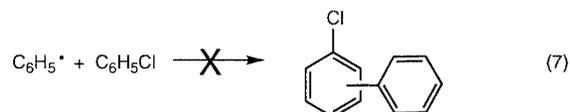
fact that batch addition of the formate gives quantitative yield of the coupling product, and practically no benzene (no reduction product) shows that the latter reaction is much slower

(i.e. $k_4 \gg k_5$). This is why a quantitative yield of biphenyl was obtained when the formate was added in batches equivalent to the amount of palladium catalyst present.

Conversely, when a sufficient amount of formate is present so that enough of the Pd^{2+} is reduced to Pd^0 , eqn. (4) becomes important and the reduction of chlorobenzene to benzene [eqn. (6)] also takes place.



No chlorobiphenyls were observed, negating the possibility of an attack of the phenyl radicals on chlorobenzene [eqn. (7)].

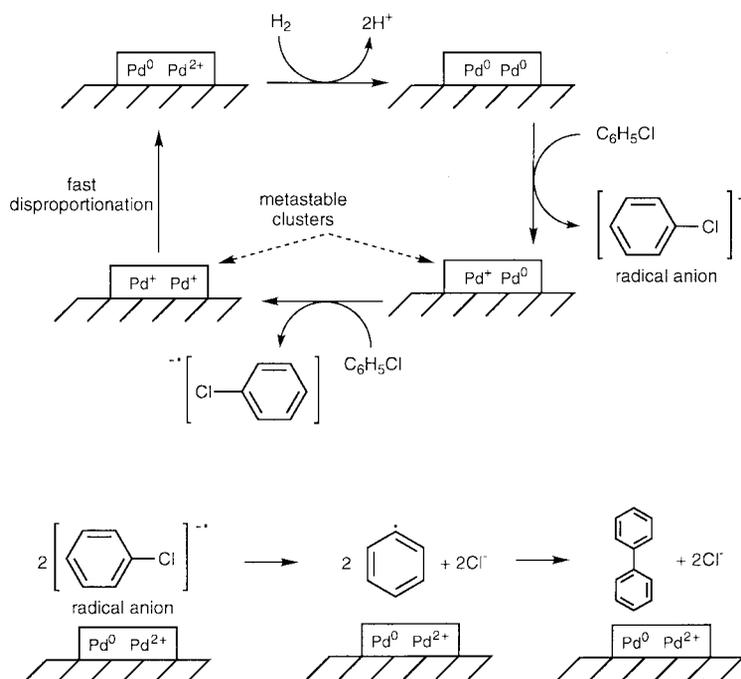


Further support for this is obtained from the fact that **2b–e** were the only coupling products observed when **1b–e** were employed as substrates.

Suggested catalytic cycle leading to aryl coupling

Aryl halides are known as effective electron acceptors in electron-transfer reactions with donors such as alkali metals, carbanions, and various organometals.⁸ By analogy to homogeneous processes with palladium and nickel complexes, the formation of a radical anion through a single electron transfer process, followed by dissociation of this radical to give a halide and an aryl radical, could represent a viable pathway for the coupling reaction observed. The catalytic cycle may begin with the coordination of a chlorobenzene molecule to the palladium cluster surface (Scheme 1, top), followed by a single electron transfer to form $[\text{C}_6\text{H}_5\text{Cl}]^{\cdot-}$ coordinated to a metastable Pd^+ cation. Because of the inherent instability of this system, after two substrate molecules interact with a palladium cluster electrons in the metal cluster would “jump” to allow the disproportionation of two Pd^{1+} atoms to Pd^0 and Pd^{2+} .

Each radical anion would now eject a chloride anion leaving behind a phenyl radical (Scheme 1, bottom). The two phenyl radicals which are still adjacent to the palladium cluster can



Scheme 1 Suggested pathways for palladium-catalyzed biaryl coupling: (top) catalytic cycle; (bottom) anion dissociation and phenyl radical coupling.

couple to form biphenyl, and Pd²⁺ can be reduced back to Pd⁰ in a reaction with one mole of dihydrogen [eqn. (3) and (4)].

Indeed, the observation of higher selectivity towards the coupling product as reaction temperature is increased can be explained by assuming that the coupling reaction (for which $E_a = 12.5 \text{ kcal mol}^{-1}$) benefits from the higher temperature, while this change is not so significant for the reduction reaction which has a lower activation energy, and indeed can occur selectively at temperatures as low as 50 °C.⁹

Support for the single-electron-transfer process proposed above can be found in the work of Munavalli *et al.* who employed an analogous system¹⁰ for the coupling of 2-chloro-3-trifluoromethylpyridine. Despite differences in reaction conditions (especially in the surfactant and PTC amounts), it may well be that dihydrogen was formed in that system, too. This would account for the formation of large amounts of 3-trifluoromethylpyridine, as these cannot be explained satisfactorily by free-radical reaction with the solvent (toluene), owing to the low quantities of benzyl-containing products observed.

The exact role played by the base in this system is still unclear.¹¹ Addition of base may facilitate the coupling reaction by neutralizing the acid produced in the reduction cycle of Pd²⁺.

Conclusions

Homocoupling of chloroaryls under moderate conditions can be achieved in the presence of a heterogeneous palladium catalyst. Competition between the reduction and coupling pathways may well depend on the concentration of available dihydrogen, which is supplied here as formate. The ease of product separation and catalyst recycling promote this method as a possible alternative to existing homogeneous catalytic coupling techniques.

Experimental

Melting points were measured in glass capillaries using an Electrothermal 9100 instrument. ¹H NMR spectra were measured on a Bruker AMX 300 instrument at 300.13 MHz. GC and GCMS analyses were performed using a HP-5890 gas chromatograph with a 50% diphenyl–50% dimethylpolysiloxane packed column (25 m × 0.53 mm). Unless stated otherwise, chemicals were purchased from commercial firms (>98% pure) and used without further purification. Products were either isolated and identified by comparison of their ¹H NMR spectra with standard samples, or identified by MS data and comparison of their GC retention times with standard samples. Reactions below 100 °C were carried out in glass apparatus, and reactions at 100 °C and above were performed in a stainless steel Parr autoclave.

General procedure for coupling of chloroaryls

Example: biphenyl **2a** from chlorobenzene **1a**. In a 300 ml stainless steel autoclave equipped with a six-bladed impeller, an external heating mantle and a gas cooling system, were placed 10.0 g (88 mmol) of **1a**, 10.0 g (150 mmol, 170 mol%) of NaHCO₂, 10.0 g (250 mmol, 280 mol%) of NaOH, 1.5–1.8 g (4–5 mmol, *ca.* 4 mol%) of CTAB, 0.85 g of 10% w/w Pd/C (0.8 mmol Pd, <1 mol%), and 40 ml H₂O. Reaction progress was monitored by GC. The autogeneous reaction pressures ranged between 1.2–1.5 atm. The mixture was stirred at 100 °C for 2 h, cooled and extracted with 40 ml of CH₂Cl₂. Solvent evaporation and recrystallizing afforded 5.63 g (83 mol% based on **1a**) of biphenyl, mp 69 °C (from cold EtOH) (lit.,¹² 69–71 °C). Found: C, 93.20; H, 6.80. C₁₂H₁₀ requires C, 93.46; H, 6.54%. δ_{H} (CDCl₃; Me₄Si) 7.37 (2H, tt, aromatic 4,4'-H), 7.46 (4H, qt, aromatic 3,3',5,5'-H), 7.61 (4H, dq, aromatic 2,2',6,6'-H), good agreement was found with literature values.¹³ The palladium

catalyst could be recycled, by vacuum filtration followed by reflux in 25 ml of MeOH, and reused.

The substituted biphenyls **2b–e** were similarly prepared: **2b** Isolated yield 20% based on **1b**, mp 75 °C (from hot EtOH) (lit.,¹⁴ 76–77 °C). Found: C, 91.31; H, 8.68. C₁₆H₁₈ requires C, 91.42; H, 8.57%. **2c** Isolated yield 75% based on **1c**, mp 75 °C (from EtOH–H₂O) (lit.,¹⁵ 93–94.5 °C). Found: C, 57.83; H, 3.05; F, 39.11. C₁₄H₈F₆ requires C, 57.93; H, 2.75; F, 39.31%. δ_{H} (CDCl₃; Me₄Si) 7.71 (8H, m, ArH) (lit.,¹⁶ 7.67). **2d** Isolated yield 20% based on **1d**, mp 175 °C (from hot EtOH) (lit.,¹² 176–177 °C). Found: C, 78.36; H, 6.80. C₁₄H₁₄O₂ requires C, 78.50; H, 6.54; O, 14.95%. δ_{H} (CDCl₃; Me₄Si) 3.84 (6H, s, 2 × OCH₃), 6.97 (4H, dt, ArH), 7.47 (4H, dt, ArH), good agreement was found with literature values.¹⁷ **2e** Isolated yield 60% based on **1e**, mp 118.5 °C (from CH₂Cl₂) (lit.,¹⁴ 120.7–121.5 °C). Found: C, 91.42; H, 7.92. C₁₄H₁₄ requires C, 92.30; H, 7.69%.

Experimental procedure for kinetic studies

Example: 88 mmol **1a**, 250 mmol NaOH, 150 mmol NaHCO₂, 0.8 mmol of 10% Pd/C and 7 mmol of CTAB were mixed in 40 ml of water at 110 °C in an autoclave (*vide supra*). Reaction progress was monitored by GC. The following parameters were studied: (i) initial substrate concentration, using xylene as the organic solvent (three experiments at 10% w/v, $k_{\text{obs}} = 3.5 \times 10^{-2} \text{ min}^{-1}$, $r^2 = 0.996$ for 7 observations; 15% w/v, $k_{\text{obs}} = 2.9 \times 10^{-2} \text{ min}^{-1}$, $r^2 = 0.996$ for 9 observations; and 20% w/v, $k_{\text{obs}} = 2.7 \times 10^{-2} \text{ min}^{-1}$, $r^2 = 0.996$ for 9 observations); (ii) catalyst loading (4 experiments using 0.25 mol% Pd, $k_{\text{obs}} = 2.4 \times 10^{-2} \text{ min}^{-1}$, $r^2 = 0.998$ for 8 observations; 0.5 mol% Pd, $k_{\text{obs}} = 2.9 \times 10^{-2} \text{ min}^{-1}$, $r^2 = 0.987$ for 7 observations; 0.9 mol% Pd, $k_{\text{obs}} = 4.1 \times 10^{-2} \text{ min}^{-1}$, $r^2 = 0.992$ for 7 observations; and 1 mol% Pd, $k_{\text{obs}} = 4.3 \times 10^{-2} \text{ min}^{-1}$, $r^2 = 0.999$ for 7 observations); (iii) reaction temperature (4 experiments at 90, 100, 110, and 120 °C); (iv) NaOH concentration (4 experiments for 1 h, at 0, 15, 25, and 35% w/v NaOH; conversions were 46, 78, 92, and 93% respectively; selectivities to **2a** were 38, 69, 87, and 87%, respectively).

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