

UC BERKELEY COLLEGE OF CHEMISTRY

CHEMISTRY 112B

ORGANIC CHEMISTRY

The Suzuki Reaction

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1 Introduction

1.1 Experimental Introduction

The Suzuki Reaction is an important type of coupling reaction, a designation that encompasses a variety of processes that combine (or “couple”) two hydrocarbon fragments with the aid of a catalyst (in the Suzuki reaction, palladium in a basic environment). The reaction is able to conjoin a variety of aryl halides and alkenyl halides with alkenylboranes and arylboronic acids¹, and is thus an important method of synthesizing many styrenes, alkenes, and biphenyls. In this lab, we carried out a textbook example of the Suzuki reaction, coupling an aryl bromide with an arylboronic acid to produce a biphenyl.

1.2 Research in this Area

Though the mechanism of the Suzuki reaction is well-established, alternate forms, derivatives, and offshoots of the reaction are discovered constantly. Because of the ubiquity of this reaction in the synthesis of many pharmaceuticals and other compounds, these discoveries expound on our knowledge of how this reaction works, and simultaneously open up new paths for synthesis or research, as described in a 2012 review paper^[4]. One such paper explores the mechanics of asymmetric cross-coupling Suzuki reactions^[2], enantioselective reactions that couple two different compounds. Because of the differing properties of enantiomers, especially pharmaceutically, enantioselective reactions are always important. Different reaction conditions of the Suzuki reaction have also been investigated; a 2002 paper shows that under specific conditions, microwave irradiation can be used to hasten the Suzuki reaction while still maintaining high yields^[3]. The Suzuki reactions’ ability to easily coordinate biaryl compounds, along with its alignment with the principles of green chemistry, make it an important and fruitful branch of organic research.

1.3 Reaction Scheme

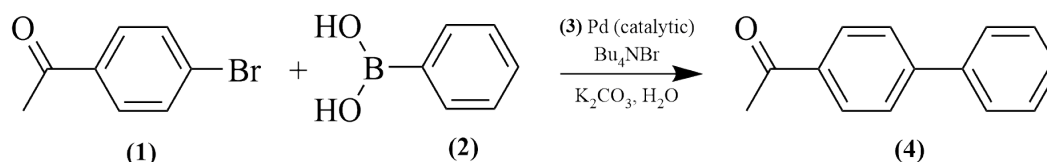


Figure 1: Overall reaction scheme of the Suzuki Cycle

¹The coupling of aryl halides or alkenyl halides with alkenylboranes was first reported by Suzuki and Miyaura in 1979; the coupling of aryl halides and arylboronic acids was expounded upon in 1981.

The Suzuki Reaction performed in class involved reacting 4-bromoacetophenone (**1**), an aryl halide, with phenylboronic acid (**2**), an arylboronic acid, to form 4'-phenylacetophenone (**4**) as a product. The reaction takes place in the presence of palladium (**3**) as a catalyst, with tetrabutylammonium bromide serving as a phase-transfer catalyst to promote interface between the aqueous and organic phase. The solution also contains potassium carbonate, to produce a basic environment for the reaction, and because of the surfactant-esque effects of tetrabutylammonium bromide, the reaction can occur in water.

1.4 Primary Reaction Mechanism

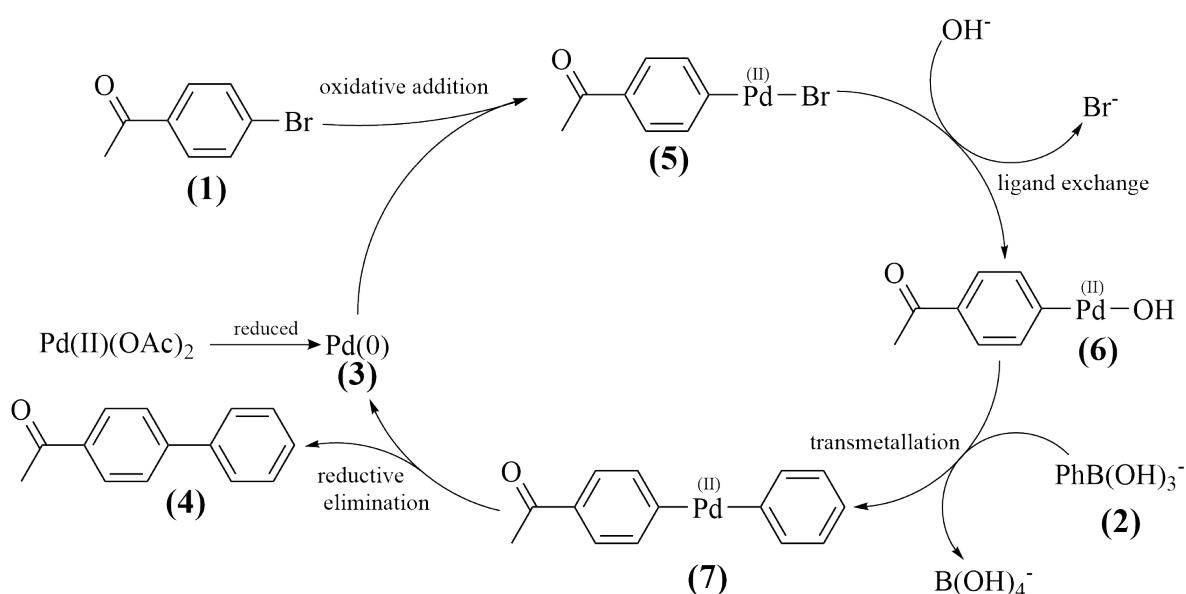


Figure 2: Reaction Mechanism of the Suzuki Cycle

The reaction begins with a palladium catalyst (**3**). The catalyst is combined with 4-bromoacetophenone (**1**) and, through a process of oxidative addition, the palladium catalyst reacts to form a bromopalladium-acetophenone complex (**5**). A ligand substitution in the basic environment produces a hydroxypalladium-acetophenone complex (**6**), which then undergoes transmetalation with phenylboronic acid (**2**), to produce a phenylpalladium-acetophenone complex (**7**). Finally, the palladium is extricated from between the two aromatics via reductive elimination, producing the 4'-phenylacetophenone product (**4**) and refreshing the palladium catalyst (**3**) for another cycle.

2 Results and Discussion

The final product created via this reaction was a grey crystal which was determined to consist mostly of the desired product (4'-phenylacetophenone) through NMR and melting-point analysis, albeit at the somewhat low percent yield of 41%. Relatively accurate NMR data, along with an acceptable melting-point range (119.4°C to 120.8°C, compared to the expected range of 117°C to 123°C), leads us to believe that the sample produced is comparatively pure, though minor discrepancies may exist. The possible sources of contamination for this experiment are limited to unreacted starting material, side products, and water contamination in the final sample due to insufficient drying. Based on the relatively clean nature of the NMR spectrum (see section 3.3 on page 6), it can be concluded that the influence of unreacted starting materials and side products on the final sample was comparatively minimal, else the NMR data would have exhibited characteristic stretches. Small quantities of unreacted water could serve to explain some minor anomalies in the NMR spectra, though melting-point analysis attests to the purity of the sample (see section 3.2 on page 5). In sum, though minute discrepancies exist in the data that could be explained by trace quantities of impurities, the product appears to be mostly pure.

The purity of the sample can be attributed to a variety of causes, not least of which is the separation procedure, which takes great pains to remove the starting products from the final sample so that they do not contaminate it. Following the 45-minute reflux of the initial reactants, filtration of the wet sample through a Hirsch funnel served to remove any water-soluble reactants (among them phenylboric acid, tetrabutylammonium bromide, and potassium carbonate, along with any boron-containing salts that may have been formed as side products). Later in the procedure, centrifugation of the sample in an acetone matrix followed by extraction of the supernatant served to isolate the product from leftover palladium catalyst, whose high density and insolubility in acetone rendered it vulnerable to separation in this manner. Between these two separation steps, the product was efficiently isolated from the starting ingredients as well as any side products that may have formed.

However, unlike the apparent purity of the sample, the percent yield of the reaction is comparatively low, and suffered from a variety of pitfalls. The largest cause for this low percent yield was undoubtedly human error: some steps of the reaction – particularly scraping solid off the sides of the round-bottom container and draining off supernatant from the centrifuged

sample – were rife with opportunities for large fractions of the sample to be left behind. Stepping outside the realm of the human, it is plausible that the reaction simply did not go perfectly to completion, though it is unlikely that this could have singlehandedly caused the large deviation from expected yield. It is far more likely that the low yield in this experiment was simply due to imperfect sample gathering and miscellaneous human mistakes (including a single minor spill); as such, the best hope for increasing the yield of this experiment would involve more meticulous laboratory practices.

3 Experimental

3.1 Methods

4'-Phenylacetophenone (4):

4-bromoacetophenone (0.199 g, 1 mmol), phenylboric acid (0.134 g, 1.1 mmol), palladium (II) acetate (3 mg), tetrabutylammonium bromide (0.322 g, 1mmol), and potassium carbonate (0.345 g, 2.5 mmol) were weighed into a 5 mL long-neck round-bottom flask, chased by 1.0 mL of distilled water (0.056 mol at $1 \frac{\text{g}}{\text{mL}}$). An apparatus was constructed, consisting of the flask attached to a condenser and capped with a septum, which was pierced with a syringe to provide pressure relief. The apparatus was heated in a sand bath for 45 minutes at a temperature of approximately 120 °C, during which time crystals of product formed in the flask. After cooling to room temperature, the solid product was scraped into a Hirsch funnel for filtration, with the aid of a 10.0 mL wash of hot water (0.56 mol at $1 \frac{\text{g}}{\text{mL}}$). The dried solid was dissolved in 3.0 mL of acetone (0.041 mol at $0.791 \frac{\text{g}}{\text{mL}}$) and the mixture was centrifuged for 2 minutes. Following centrifugation, the supernatant was separated out and boiled down to 2 mL on a sand bath. Crystals were precipitated in the solution using water, at which point the tube was cooled to 0 °C, and the crystals were washed and dried. The dried crystals were weighed until a consistent mass was received, and the melting point of the final 4'-phenylacetophenone (also known as 4-acetylbiphenyl) product was calculated. 0.80 g (0.408 mmol) of product were recovered, producing a final percent yield of 41% ($\frac{0.80\text{g} \times \frac{1\text{mol}}{196.24\text{g}} \text{ actual}}{1 \times 10^{-3} \text{mol expected}}$).

3.2 Melting Point Analysis

Melting-point analysis, though fairly qualitative in nature, reveals that the final sample is reasonably pure. While the observed melting point of 4'-phenylacetophenone ranges from 117 °C

to 123 °C [1], the sample began to melt at 119.4 °C and finished melting at 120.8 °C . As a result, it can be concluded that the sample most likely consists of rather pure 4'-phenylacetophenone, though the possibility that there exist impurities with a coincidentally similar melting point cannot be discounted.

3.3 Product ¹H NMR analysis

The ¹H NMR obtained for the recrystallized product is: (400 MHz, CDCl₃) δ 2.64 (s, 3H), 7.40 (t, J = 7.6, 1H), 7.47 (t, J = 7.4, 2H), 7.63 (d, J = 8.0, 2H), 7.69 (d, J = 8.8, 2H) and 8.03 (d, J = 8.4, 2H). The relative lack of obfuscation in this NMR, along with the relatively clean splitting (singlets, doublets, and triplets are fairly recognizable in expected positions) corroborates the belief that our final product is of relatively high purity.

4 Conclusion

In this lab, we successfully performed the Suzuki reaction, using a palladium catalyst to couple an arylboronic acid and an aryl halide. Although our yield left much to be desired, our product displayed a reasonably high purity, as determined by ¹H NMR and melting-point analyses. In sum, this lab provided excellent practice for experimental and analytical techniques, and provided a detailed look into a key reaction that is still actively researched today.

References

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- [2] Cammidge, A. N.; Crépy, K. V. L. The first asymmetric Suzuki cross-coupling reaction. *Chem. Commun.* [Online] **2000**, 18, 1723-1724.
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AVQ-400 QNP Proton starting parameters. 7/16/03. Revised 7/22/03 RN

