

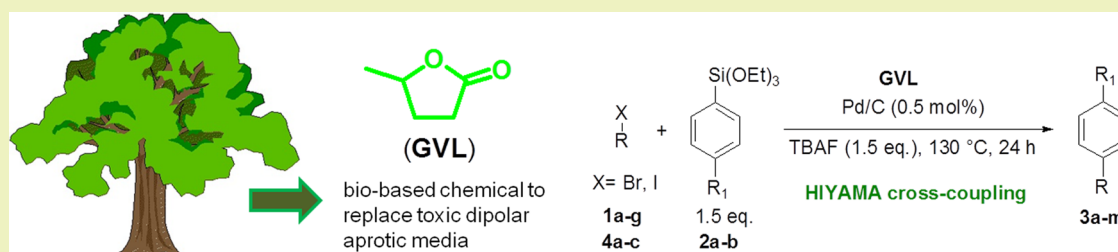
γ -Valerolactone as a Renewable Dipolar Aprotic Solvent Deriving from Biomass Degradation for the Hiyama Reaction

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S Supporting Information



ABSTRACT: γ -Valerolactone (GVL) can be a valid biobased replacement for toxic dipolar aprotic solvents especially in widely used cross-coupling reactions. In this contribution, we have proved that GVL can be a useful medium for the Hiyama reaction, and we developed a practical and efficient protocol for the Hiyama coupling using a nonexpensive and commercially available heterogeneous palladium catalyst without the use of any ligand or additive. Desired cross-coupling products **3a–m** have been obtained in good to excellent yields (74–94%).

KEYWORDS: γ -Valerolactone, Hiyama reaction, Renewable feedstock, Green chemistry, Safer media

INTRODUCTION

In recent years much attention has been devoted to biomass as a renewable feedstock source of carbon to obtain valuable chemicals and replace those derived from oil processing.¹ The representative examples are biofuels, platform chemicals, and different solvents and reagents. For the actual development of an efficient biorefinery strategy, it is important to identify all the possible applications where biobased chemicals can be used and prove the real efficiency of biomass-derived materials as alternatives for those obtained from petroleum.

Recently, particular attention has been focused on γ -valerolactone (GVL).² This substance can be easily obtained from lignocellulosic biomass,³ and it shows ideal properties that make it attractive for being used in energy production or as renewable carbon-based consumable products.⁴ Moreover, although only sporadically, GVL has been used as a solvent to replace classic organic media.⁵ Considering its physical properties,⁶ in our opinion, it is a particularly promising chemical to replace classic dipolar aprotic media that are routinely used in various key processes in both academia and industry, for example, cross-coupling reactions, nucleophilic substitutions, etc. Currently, this class of solvents is under strict law regulations,⁷ and the identification of a nontoxic and efficient chemical for its efficient replacement is timely.⁸

We are currently investigating our hypothesis that GVL could be a safe and efficient biomass-derived dipolar aprotic solvent.

We have been contributing to the development of an efficient and sustainable approach to organic synthesis by investigating the use of unconventional reaction media such as azeotropic mixtures⁹ or solvent-free conditions,¹⁰ and we have also exploited flow conditions in order to develop novel synthetic procedures featuring minimal waste production and high chemical efficiency.¹¹

Recently, we have directed our attention to cross-coupling reactions, such as the Hiyama reaction, which are extremely useful and widely employed chemical processes. The Hiyama reaction is a palladium-catalyzed cross-coupling reaction that allows preparation of symmetrically and nonsymmetrically substituted biaryls by coupling organosilanes and arylhalides or pseudohalides.¹² This reaction received limited attention in the past in comparison with other cross-coupling reactions, such as Suzuki, Stille, Negishi, or Sonogashira coupling. However, in the past few years, renewed attention to the Hiyama reaction has commenced thanks to the development of new synthetic approaches toward organosilane compounds.^{13–15} Moreover, the Hiyama reaction has many advantages with respect to other coupling reactions¹⁶ such as retention of regio- and stereochemistry during coupling¹⁷ and low toxicity of both the starting organosilane and organosilane byproduct.¹⁸ Taking

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into account the great potential of this reaction, it is important to study the scope and limitations, as well as to develop sustainable protocols for this transformation.

The Hiyama reaction is usually performed in the presence of a fluoride source, such as tetrabutylammonium fluoride (TBAF),^{19–29} CsF,^{30,31} or KF.³² Fluoride plays an important role of preactivating the less nucleophilic organosilane compound by forming a more reactive pentavalent silicon species, which undergoes a transmetalation step during the reaction by palladium.¹⁸ Another manner to activate the organosilane compound for the transmetalation step is to use an inorganic base, such as KOH, NaOH or K₂CO₃, in water media.^{33–37} Very often, ligands^{19,21,23,24,27,29,38} and additives^{20,26,28} are used in the Hiyama reaction to reach good reactivity or to avoid the formation of side products. Most importantly for the scope of this work, the reaction is performed in classic polar aprotic solvents such as DMF^{21,25,31,32,38} or in petroleum-derived media such as toluene,^{20,23,24,26,27} dioxane,²⁹ or THF.^{19,22,27}

In this contribution, we report our efforts to develop a sustainable protocol for the Hiyama reaction based on the use of GVL as a nontoxic biomass-derived polar aprotic solvent and by using palladium on activated charcoal (Pd/C) as a nonexpensive and easily recoverable heterogeneous catalyst.

EXPERIMENTAL SECTION

General Procedure for Hiyama Reaction. In a screw capped vial equipped with a magnetic stirrer, Pd/C 10% wt (5.3 mg, 0.5 mol %), GVL (1 mL), TBAF (488 mg, 1.5 mmol), and 1-bromo-4-nitrobenzene (**1a**) (204 mg, 1 mmol) were consecutively added, and the resulting mixture was degassed with argon. Then triethoxy(phenyl)silane (**2a**) (368 mg, 0.369 mL, 1.5 mmol) was added, and the mixture was heated at 130 °C under an atmosphere of argon. After 24 h, the reaction mixture was cooled to room temperature, and 4 mL of water was added. The formed precipitate was filtered off, washed with 4 mL of water, and purified by column chromatography (petroleum ether:EtOAc, 95:5). **3a** was obtained as a white solid (165 mg, 83% yield).

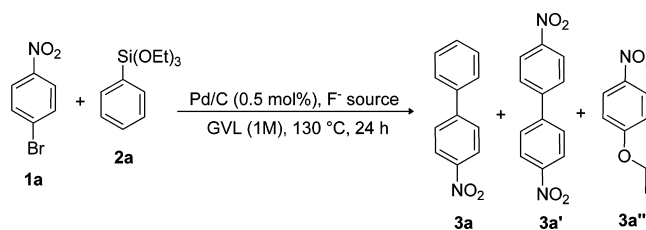
RESULTS AND DISCUSSION

GVL has been used as the medium for the representative Hiyama reaction between 1-bromo-4-nitrobenzene (**1a**) and triethoxy(phenyl)silane (**2a**) (reaction shown above Table 1). Several different fluoride sources, such as KF, CsF, and tetrabutylammonium fluoride (TBAF), were considered to identify the best reaction conditions. From the data obtained in Table 1, we found that the best fluoride source is TBAF (Table 1, entry 3), while KF and CsF did not show appreciable reactivity (Table 1, entries 1 and 2). Using 2 equiv of TBAF, **1a** reacted completely but with the formation of 9% of 4,4'-dinitro-1,1'-biphenyl (**3a'**), and 17% of 1-ethoxy-4-nitrobenzene (**3a''**) as byproducts.

Formation of **3a'** is generally reported and derives from the homocoupling reaction of 1-bromo-4-nitrobenzene (**1a**). Similarly, formation of byproduct **3a''** is also known and can be explained by the nucleophilic substitution of bromide by an ethoxide anion generated from phenyltriethoxysilane (**2a**) by TBAF.²⁸ These chemical results and product distribution in the Hiyama reaction are known and are typical of such processes.²⁶ Improvements can be achieved by using additional chemicals. For example, a side reaction leading to **3a''** is generally suppressed using an additive such as acetic acid.²⁸

When TBAF was reduced to 1.2 equiv to minimize the formation of **3a''**, sufficient activation of **2a** could not be

Table 1. Optimization of Reaction Conditions for the Hiyama Coupling of 1-Bromo-4-nitrobenzene (1a**) and Triethoxy(phenyl)silane (**2a**)**



| entry | silane (eq) | activator (eq) | conversion of 1a (%) ^a | products ratio 3a/3a'/3a'' |
|----------------|-------------|---|--|-----------------------------------|
| 1 | 1.2 | KF (2) | 10 | – |
| 2 | 1.2 | CsF (2) | 0 | – |
| 3 | 1.2 | TBAF (2) | 100 | 74/9/17 |
| 4 | 1.2 | TBAF (1.2) | 100 | 80/20/0 |
| 5 | 1.2 | TBAF (1.5) | 100 | 80/10/10 |
| 6 | 1.5 | TBAF (1.5) | 100 | 91/9/0 |
| 7 ^b | 1.5 | TBAF (1.5) | 100 | 85/15/0 |
| 8 ^c | 1.5 | TBAF (1.5) | 80 | 91/9/0 |
| 9 ^d | 1.5 | TBAF (1.5) | 90 | 92/8/0 |
| 10 | 1.5 | K ₂ CO ₃ (1.5) | 0 | – |
| 11 | 1.5 | K ₂ CO ₃ (1.5) (DMF) | 43 | 29/48/23 |
| 12 | 1.5 | K ₂ CO ₃ (1.5) (H ₂ O) | 0 | – |

^aRemaining material was unreacted **1a**. ^bReaction performed at 150 °C. ^cReaction performed at 110 °C. ^dReaction performed with 0.1 mol % of Pd/C.

reached, and the desired product **3a** was formed together with a consistent amount of **3a'** (homocoupling product) (Table 1, entry 4). Increasing the TBAF amount to 1.5 equiv led again to the formation of **3a''** (Table 1, entry 5).

The best reaction conditions were reached by using an increased amount of **2a** (1.5 equiv). Under these conditions, without the use of any additive, **3a''** formation was completely suppressed, and only **3a'** was formed (9%) (Table 1, entry 6). Changes in the reaction temperature led to no improvement. In fact, an increase in temperature brought an increase in the homocoupling product **3a'** (Table 1, entry 7), and a decreasing in temperature brought incomplete conversion (Table 1, entries 8) as did the decrease in the catalyst amount (Table 1, entry 9). Moreover, we tried to activate **2a** with an inorganic base such as potassium carbonate instead of a fluoride source and obtained an unsatisfactory conversion (Table 1, entry 10). Similarly, in DMF, the system showed low reactivity and low selectivity (Table 1, entry 11), while in water, no conversion at all was observed.³⁹

Use of 0.5 mol of Pd/C and 1.5 equiv of TBAF at 130 °C were therefore identified as the best reaction conditions.

The protocol was extended to a variety of aryl bromides (**1a–g**) and aryl iodides (**4a–c**) (Table 2) using as coupling partners triethoxy(phenyl)silane (**2a**) and triethoxy(4-methoxyphenyl)silane (**2b**).⁴⁰

Several biaryls (**3a–m**) were prepared with good to excellent yield (74–94%). In our reaction conditions, both deactivated bromide, with electron donor substituents such as 4-bromotoluene (**1c**) and 4-bromoanisole (**1g**), and more activated substrates possessing electron-withdrawing substituents such as 1-bromo-4-nitrobenzene (**1a**), 4'-bromoacetophenone (**1e**), and 3'-bromoacetophenone (**1f**) reacted equally well providing the corresponding coupling products in good yields. On the other hand, the use of substituted silanes such as

Table 2. Synthesis of Different Substituted Biaryls 3a–m

| entry | X | R | R ₁ | product | isolated yield (%) |
|-------|----|---|----------------|---------|----------------------|
| 1 | Br | (4-NO ₂)C ₆ H ₄ - (1a) | -H (2a) | 3a | 83 (85) ^a |
| 2 | I | (4-NO ₂)C ₆ H ₄ - (4a) | -H (2a) | 3a | 78 |
| 3 | Br | C ₆ H ₅ - (1b) | -H (2a) | 3b | 94 |
| 4 | I | C ₆ H ₅ - (4b) | -H (2a) | 3b | 92 |
| 5 | Br | (4-Me)C ₆ H ₄ - (1c) | -H (2a) | 3c | 86 (65) ^a |
| 6 | I | (4-Me)C ₆ H ₄ - (4c) | -H (2a) | 3c | 80 |
| 7 | Br | naphthyl- (1d) | -H (2a) | 3d | 82 |
| 8 | Br | (4'-COCH ₃)C ₆ H ₄ - (1e) | -H (2a) | 3e | 78 (81) ^a |
| 9 | Br | (3'-COCH ₃)C ₆ H ₄ - (1f) | -H (2a) | 3f | 74 |
| 10 | Br | (4-OMe)C ₆ H ₄ - (1g) | -H (2a) | 3g | 78 (77) ^a |
| 11 | Br | C ₆ H ₅ - (1b) | -OMe (2b) | 3g | 81 |
| 12 | I | C ₆ H ₅ - (4b) | -OMe (2b) | 3g | 80 |
| 13 | Br | (4-Me)C ₆ H ₄ - (1c) | -OMe (2b) | 3h | 81 |
| 14 | I | (4-Me)C ₆ H ₄ - (4c) | -OMe (2b) | 3h | 80 |
| 15 | Br | (4-OMe)C ₆ H ₄ - (1g) | -OMe (2b) | 3i | 91 |
| 16 | Br | (4-NO ₂)C ₆ H ₄ - (1a) | -OMe (2b) | 3j | 81 |
| 17 | I | (4-NO ₂)C ₆ H ₄ - (4a) | -OMe (2b) | 3j | 78 |
| 18 | Br | naphthyl- (1d) | -OMe (2b) | 3k | 79 |
| 19 | Br | (4'-COCH ₃)C ₆ H ₄ - (1e) | -OMe (2b) | 3l | 75 (90) ^a |
| 20 | Br | (3'-COCH ₃)C ₆ H ₄ - (1f) | -OMe (2b) | 3m | 80 |

^aIn the bracket is the reported yield in ref 26.

2b did not influence negatively the reactivity of the system, and constantly good results with activated or deactivated substrates were obtained confirming the wide application for this protocol.

Aryl iodides showed a comparable reactivity, although showed a higher tendency to homocoupling with a constantly lower yield of the desired coupling products (Table 2, entry 1 vs 2, entry 5 vs 6, or entry 16 vs 17). In addition, it should also be noticed that our results are satisfactorily comparable to those reported in the literature using a similar protocol with Pd/C as catalyst and TBAF as activator without any additional ligand²⁶ (Table 2, entries 1, 5, 8, 10, 19).

In conclusion, we demonstrated that GVL can be an efficient medium for the Hiyama reaction. We developed a practical and efficient protocol by using a nonexpensive heterogeneous palladium catalyst, avoiding the use of any ligands or additives. The desired cross-coupling products **3a–m** have been obtained in good to excellent yields. These data prove that GVL is a good biomass-based solvent and in our opinion is very promising for its use in industrial and academic applications. Further investigations are ongoing to prove its use as a general alternative to common toxic dipolar aprotic media.

■ ASSOCIATED CONTENT

📄 Supporting Information

Full characterization of compounds **3a–m** and copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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