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Deep Eutectic Solvents as Reaction Media for the Palladium-Catalysed C-S bond formation. Scope and Mechanistic Studies

Xavier Marset,^[a] Gabriela Guillena*^[a] and Diego J. Ramón*^[a]

Abstract: A unique jigsaw catalytic system based on deep eutectic solvents, and palladium nanoparticles where C-S bonds are formed from aryl boronic acids and sodium metabisulfite, is introduced. The functionalization step compatible with a broad spectra of reagents such as nucleophiles, electrophiles or radical scavengers. This versatile approach allows the formation of different type of products in an environmentally friendly medium by selecting the components of the reaction, which engage one with another as pieces in a jigsaw. This simple procedure avoids the use of toxic VOCs as solvents, allowing the formation of complex molecules in a one pot reaction under mild conditions. Despite that only 1 mol% of metal loading is used, the recyclability of the catalytic system is possible. Kinetic experiments have been performed and the reaction order for all reagents, catalyst and ligand was determined. The obtained results were compared to palladium nanocrystals of different known shapes in order to shed some light on the properties of the catalyst.

Due to the constantly growing importance of sustainability, the use of simple and versatile protocols for the synthesis of complex molecules is a main goal in chemistry. While planning a synthetic pathway to achieve a product, factors like selectivity, waste production, toxicity, energy or the overall number of synthetic steps should be taken into account to design an efficient transformation.¹ New strategies such as multicomponent reactions (MCRs),² diversity oriented synthesis (DOS)³ or multiple bond-forming transformations (MBFTs)⁴ are tools which try to maximize all these aspects. Nevertheless, in most cases the scope of this kind of approaches is quite limited, not being extensible for the synthesis of related substructures.

Approaches in which reagents of different nature, such as electrophiles, nucleophiles and radicals are assembled in order to obtain a complex molecule along with all these previous concepts like pieces in a jigsaw must be urgently addressed.

Sulfones, interesting in drug industry,⁵ or as intermediates in the total synthesis of complex molecules,⁶ are a clear example in which a sustainable approach is demanded. Methodologies for their synthesis such as sulfide oxidation,⁷ alkylation of sulfinate salts,⁸ palladium-catalyzed insertion of SO₂,⁹ or use of DABSO under Pd or Au catalysis¹⁰ suffered severe limitations related to reagents, substrates and products scope.

More readily available K₂S₂O₅ can be used as a SO₂ source, under Pd¹¹ or Au¹² catalysis (5-10 mol%), but due to the poor solubility of the inorganic salt in the organic media a limited scope

was obtained. Moreover, aryl sulphides can be obtained via C-H functionalization by a thiolation of phenol or phenylamine derivatives mediated by iodine using a sulfinate salts as intermediates.¹³

Deep Eutectic Solvents (DESs) have emerged as an environmentally benign alternative to hazardous organic solvents, as they are available, non-toxic, biodegradable, recyclable, non-flammable, renewable and cheap being considered a green solvent.¹⁴ Their properties, such as conductivity, viscosity, vapour pressure and thermal stability can be fine-tuned by the appropriate choosing of the mixture components.¹⁵ Furthermore, due to the nature of the reaction media, all the inorganic salts and organic reagents would become soluble, with precedents of organosulfur compounds being compatible with DES media, having being employed in simple organic transformations.¹⁶

With these precedents, the sulfonylation reaction of phenylboronic acid (**2a**) with sodium metabisulfite (**3**) as SO₂ source was tested. Pentyl bromide was added from the beginning of the reaction, performing the sulfonylation and subsequent alkylation of the sulfinate salt in one pot. Best result was obtained using a mixture of choline chloride (ChCl) and acetamide with only 1 mol% of PdCl₂. Since a phosphine ligand seems to be necessary for the reaction to proceed at good reaction rates, we decided to use recently reported phosphine ligand **1**¹⁷ (3 mol%, Table S1, Chart 1). Other possible safe sources of SO₂ were also tested (Table S2) as well as alternative aryl sources (Table S3), but none of them improved the result obtained with sodium metabisulfite and phenylboronic acid. Despite the good results obtained with palladium chloride, other metallic catalysts were tested (Table S4). It should be noticed that the inexpensive FeCl₂ also afforded the desired product **5a** in a 90% yield (Chart 1, footnote b). Changing the ligand/metal ratio to 1:1 in order to obtain a more active Pd(I) species did not improve the reaction yield.¹⁸

The unique properties of DES, allowed the catalytic system to be recycled, using 2-MeTHF as a sustainable VOC.¹⁹ Products were extracted, while the catalyst remained in the DES phase. The reaction was repeated 3 times by the addition of fresh reagents, without adding more metal, ligand or solvent. without a significant decrease in the reaction yield (Figure 1), achieving an accumulate TON of 279, much higher than the previous reports using K₂S₂O₅ as SO₂ source, ranging from 6.6 to 15.8.^{11,12}

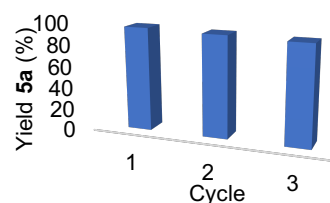
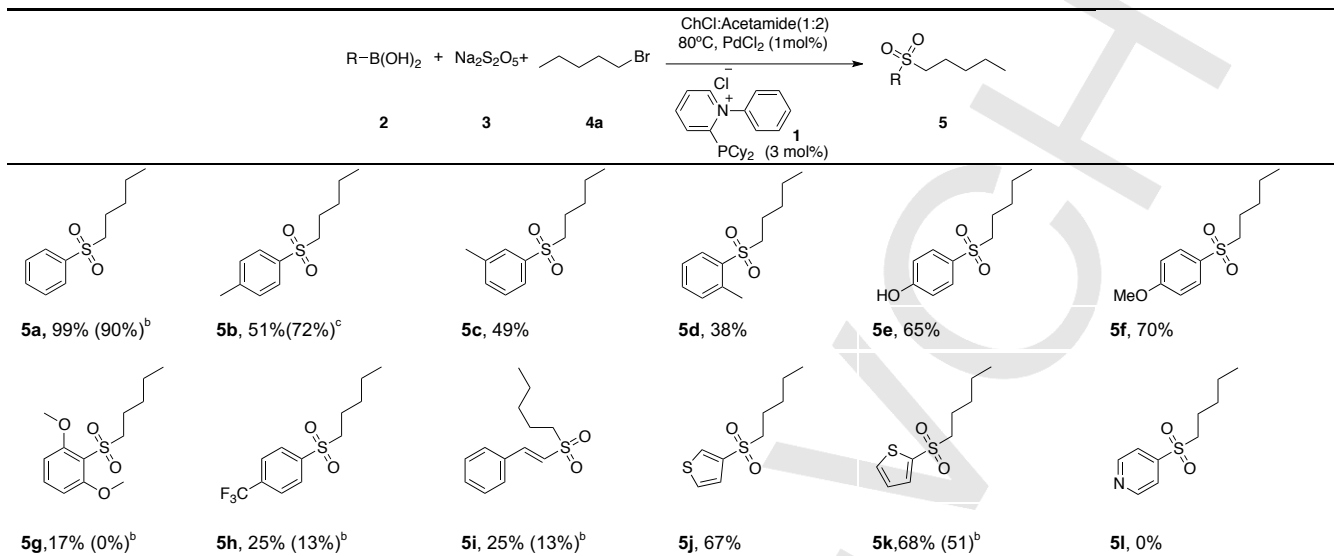


Figure 1. Recyclability study.

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 characterization data, ¹H-NMR and ¹³C-NMR data. See DOI: xxxxx

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Chart 1. Scope of boronic acids.^a

^a Reaction carried out using compounds **2** (1.0 mmol), **3** (2.2 mmol) and **4a** (2.0 mmol) in 2 mL of DES. ^b Reaction carried out using FeCl₂ (1 mol%) instead of PdCl₂. ^c Reaction carried out using 3.0 mmol of ArB(OH)₂, 6.6 mmol Na₂S₂O₅ and 1.0 mmol of C₅H₁₁Br. Isolated Yields.

Table 1. Scope of electrophiles.^a

$$\text{C}_6\text{H}_5\text{B(OH)}_2 + \text{Na}_2\text{S}_2\text{O}_5 + \text{E}^+ \xrightarrow[\text{PCy}_2 \text{ (3 mol\%)}]{\text{ChCl:Acetamide (1:2), 80^\circ\text{C}, \text{PdCl}_2 \text{ (1 mol\%)}}$$

$$\text{C}_6\text{H}_5\text{SO}_2\text{E}$$

2a **3** **4** **1** **6**

Entry	Electrophile	Product	No	Yield (%) ^b	Entry	Electrophile	Product	No	Yield (%) ^b
1			5a	99	8			6g	35
2			6a	31	9			6h	16
3			6b	42	10			6i	10 (46) ^c
4			6c	29	11			6j	38 (99) ^c
5			6d	30	12			6k	57

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Table 1. Scope of electrophiles.^a (Continued)

6		6e	33	13		6l	13 (41) ^c
7		6f	98	14		6m	98

^a Reaction carried out using compounds **2a** (1.0 mmol), **3** (2.2 mmol) and **4** (2.0 mmol) in 2 mL of DES. ^b Isolated yields. ^c Reaction carried out using 3.0 mmol of ArB(OH)₂, 6.6 mmol Na₂S₂O₅ and 1.0 mmol of electrophile.

Under optimized conditions, the scope of boronic acids was evaluated (Chart 1). The reaction gave moderate to good yields with electron-donating substituents (products **5b-5f**), while sterically hindered or electron-acceptor substituents afforded lower yields (products **5g-5i**). On the other hand, heteroaromatic boronic acids were tested, obtaining good yields with thienyl moieties. In order to prove the versatility of the synthesis, other electrophiles were tested (Table 1). The reaction proved its versatility for alkyl halides (entries 1-5). Product **6c** (entry 4) was obtained in a moderate yield, demonstrating that the mechanism of the latest step of the reaction does not occur *via* a radical pathway. Less conventional electrophiles as diaryliodonium salts can be employed (entry 6). 2-Chlorobenzothiazole afforded product **6f** with excellent yield (entry 7). Electron-poor aryl halides (entries 8-9) and alkenes (entries 10-13) can be also used as electrophiles. Finally, the use of H₂N-OSO₃H afforded the corresponding sulfonamide (entry 14).

The versatility of this process was showed by adding molecular iodine to the aryl sulfinate salt, that in a protic media gives the corresponding thiol or disulfide,²¹ acting now as electrophile. In this way, a three steps process-transformation was performed in one pot (formation of the sulfinate salt, transformation to thiol derivative and reaction with nucleophiles). The obtained results are shown in Table 2, showing moderate to good yields using phenol derivatives (entries 1-3), *N,N*-dimethylaniline (entry 4), 1,3,5-trimethoxybenzene (entry 5) or even indole (entry 6).

Also a radical process can take place in this new reaction media (Table 3), affording the corresponding disulfide (entries 1-2). If a hydroxy-functionalized alkene is added, the double bond reacts with the radical thiol with a subsequent cyclization to afford products **8c-8e** (entries 3-5).^{8c} Another radical-mediated reaction is the synthesis of **8f** from phenylpropionic acid catalyzed by phosphoric acid.^{20b}

Intrigued by the unique properties of this catalytic system, the evolution of the reaction between phenylboronic acid (**2a**) and sodium metabisulphite (**3**) to form sodium benzenesulfinate was evaluated (Figure S1). Assuming a simple equation rate and that the reaction conditions allow a pseudo-first order approximation for all reagents, the equation rate can be expressed as $\ln r_{oi} = a \ln [A]_{oi} + k$, where $[A]$ is the initial concentration of reagent. Therefore, we could estimate the reaction order for the reagents by the estimation of the reaction rate for each trial and their representation. For both reagents, PhB(OH)₂ and Na₂S₂O₅, we obtained a value very close to 1.

Table 2. Scope of aryl sulfides.^a

Entry	Nucleophile	Product	Yield (%) ^b
1			70
2			79
3			45
4			83
5			84
6			63

^a Reaction carried out using compounds **2a** (1.0 mmol), **3** (2.2 mmol) in 2 mL of DES during 12h, then I₂ (2 mmol) was added and stirred for 20 min and finally phenol/aniline derivative (2 mmol) was added and stirred for 12h at 80°C. ^b All examples are shown with yields of isolated product.

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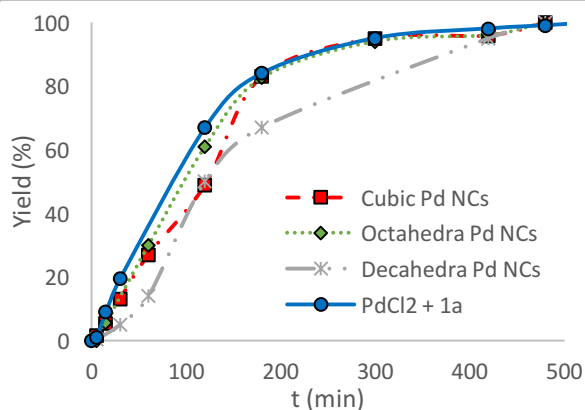
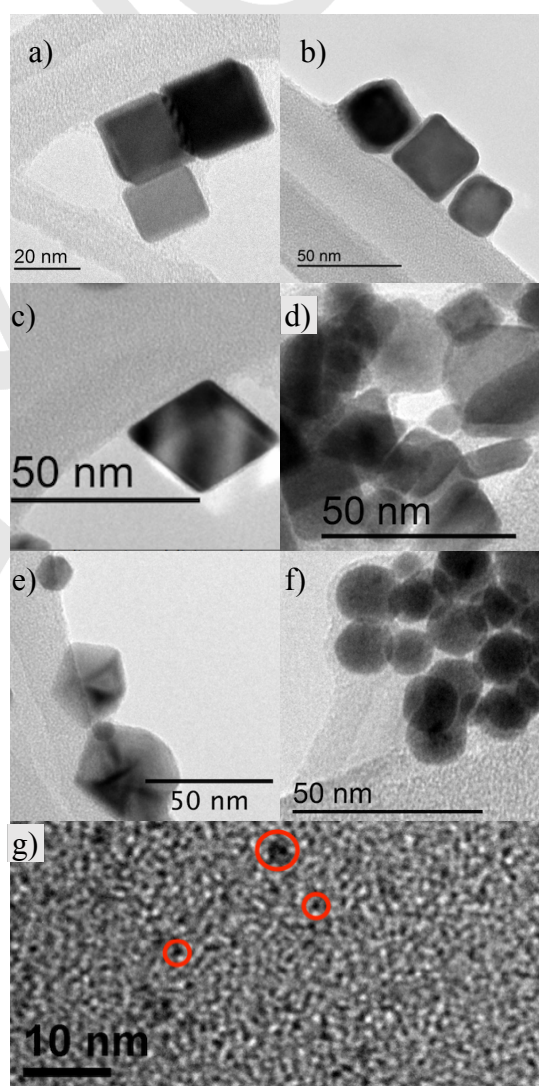
Table 3. Scope using radical scavengers.

		1) PdCl ₂ (1 mol%) 1 (3 mol%) ChCl:Acetamide (1:2), 80°C, 12h		
ArB(OH) ₂ + Na ₂ S ₂ O ₅		2) I ₂ 20 min 3) Radical Scavenger (R), 12h		Ph-S-R
Entry	Radical Scavenger	Product		Yield (%) ^a
1	-		8a	95 ^b
2	-		8b	66 ^b
3			8c	62 ^b
4			8d	42 ^b
5			8e	98 ^b
6	Ph-C≡C-CO ₂ H		8f	32 ^c

^a All examples are shown with yields of isolated product. ^b reaction carried out using compounds **2a** (1.0 mmol), **3** (2.2 mmol) in 2 mL of DES during 12h, then I₂ (2 mmol) was added and stirred for 20 min and finally enol (2 mmol) was added and stirred for 12h at 80°C. ^c Instead of I₂, Phenylpropionic Acid (2 mmol) and H₃PO₄ (4 mmol) were added to the reaction media after 8h and the reaction proceeded for 16h.

On the other hand, for the determination of the reaction order of the ligand and catalyst a graphical method was employed,²² founding a zero-order dependence for the ligand (Figure S2). This fact suggest that the ligand plays a key role in the formation of the Pd(0) nano-catalyst, but not in the rate-determining step of the reaction.²³ The order for the catalyst was found to be 0.25, indicating a not simple reaction mechanism.

Furthermore, since Pd nanoparticles are formed during the reaction, we prepared different shaped palladium nanocrystals (Pd NCs) in order to evaluate their activity and compare it with our catalytic system (Figure 2).²⁴ The highest activity was achieved with the nanoparticles obtained from PdCl₂ and cationic phosphine ligand **1**, followed by the octahedral, cubic and finally decahedral ones. Decahedral particles are reported to be very stable, with almost a spherical structure, which may explain its lower activity. On the other hand, the activity of the cubic and octahedral particles was very similar, being the octahedral slightly more active, probably due to the exposed surface facets {1 1 1} in front of the ones on the cubic nanoparticles {1 0 0}.

**Figure 2.** Plot time-yield for different shaped Pd NCs and reaction carried out with PdCl₂ + **1**.**Figure 3.** TEM images corresponding to palladium nanoparticles a) cubes b) cubes after reaction c) octahedron d) octahedron after reaction e) decahedron f) decahedron after reaction g) PdCl₂ + **1a** after reaction.

After the reaction, NCs were recovered and analyzed, with average sizes kept in the same range (See TEM in Table S5). Regarding the shape, the well-defined facets were slightly lost,

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due to leaching processes (Figure 3). The crude TEM of our standard catalytic system (PdCl₂ and ligand **1**), showed Pd clusters of 0.8 nm of average size, with around 14 Pd atoms.²⁵ In such small particles, the electronic structure seems to play a key role, with high surface area/volume ratio explaining its higher activity. This can be correlated with the reaction order obtained for PdCl₂, which was found to be 0.25, suggesting maybe that only ¼ of the Pd atoms are catalytically active, which means that in a 14-atom palladium cluster, only around 3 atoms have catalytic activity.²²

Conclusions

In conclusion, DES, PdCl₂ and ligand **1** can be efficiently applied to the jigsaw synthesis of molecules containing new C-S bonds, starting from aryl boronic acids and sodium metabisulfite, which undergo subsequent transformations in one-pot manner, reacting with nucleophiles, electrophiles and radical scavengers to afford sulfones and aryl sulfides. Furthermore, the catalytic system could be recycled up to three times without a decrease in the yield of the reaction. The high activity seems due to the very small size of nanoparticles but not to the shape.

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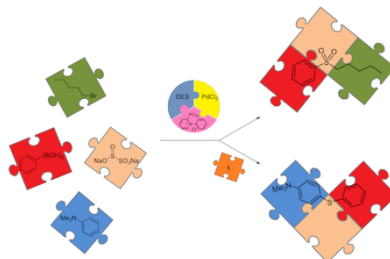
Keywords: Green Chemistry • Palladium • Solvent Effects • Sulfur • Multicomponent Reactions

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A new process concept: a unique catalytic system, where C-S bonds are formed from aryl boronic acids and sodium metabisulfite, is introduced. The functionalization step is compatible with nucleophiles, electrophiles or radical scavengers and principles of green chemistry, as in a jigsaw. Kinetic experiments have been performed, comparing results to palladium nanocrystals of different known shapes in order to shed some light on the properties of the catalyst.



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