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# Ligand-free Bio-inspired Suzuki–Miyaura Couplings using Aryltrifluoroborates as Effective Partners in Deep Eutectic Solvents

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Dedication ((optional))

**Abstract:** Pd-catalysed Suzuki–Miyaura cross-couplings between (hetero)aryl halides (Cl, Br, I) and versatile, moisture-stable mono- and bifunctional potassium aryltrifluoroborates proceed efficiently and chemoselectively in air and under generally mild conditions, with a catalyst loading as low as 1 mol%, in the absence of additional ligands, and employing $Na_2CO_3$ as base, and the deep eutectic solvent (DES) choline chloride/glycerol (1:2) as a sustainable and environmentally responsible medium. Catalyst, base and DES have been easily and successfully recycled up to six times with an E-factor as low as 8.74. Valuable biaryls and terphenyl derivatives were furnished in yields of up to and above 98%; over 50 cases have been compared and discussed. The methodology was also applied to the synthesis of the non-steroidal anti-inflammatory drugs Felbinac and Diflunisal.

## Introduction

Among the wealth of transition-metal catalysed cross-coupling reactions in the arsenal of chemical practitioners, the Suzuki–Miyaura (SM) coupling has served over the last two decades as one of the most versatile and powerful strategies for achieving C–C bond formation because of the low toxicity and easy availability of boron reagents, the usually mild reaction conditions, and the tolerance of a wide range of functional groups. These couplings are generally run under *homogeneous conditions* with various ligands, typically in hazardous and toxic volatile organic compounds (VOCs) (e.g., toluene, DMF), thereby have a heavy environmental impact. Thus, intense research efforts have been made to develop protocols of more ecological relevance. These include the use of neat water, usually with phase-transfer catalysts, water-soluble phosphines, pseudo-halides as electrophilic partners, and harsh heating.[1] Aqueous solvent systems have alternatively been investigated to overcome pitfalls experienced when poorly water-soluble and poorly water-stable substrates and/or catalysts are used.[2] In the absence of ligands and/or specific solid-supported palladium catalysts, however, the coupling of the readily available and low-cost aryl chlorides still poses challenges also in these media.[2b,c,h,i] Significant eco-friendly enabling technologies relying on microwaves, ultrasound, mechanochemistry, light, and flow chemistry have also progressed impressively in recent years.[3]

SM reactions are usually carried out utilising boronic acids or boronate ester analogues. Disadvantages in the use of organoboranes are (a) their propensity towards aerobic oxidation, with decreased yields if the solvent is not degassed, (b) dehydroboration and protodeboronation processes, which imply the use of excess reagents to drive the reaction to completion, and (c) Pd-catalysed homocoupling reactions.[4] Arylboronic acids, jointly with aryl bromides and iodides, are still the partners of choice in the reported examples of Pd-catalysed SM couplings conducted either in biomass-derived solvents[5a–g] or in ionic liquids (ILs).[5h] As for the former, with the exception of ethyl lactate[5b] and glycerol derivatives,[5c] such couplings have always been accomplished in the presence of soluble phosphines and under harsh heating (100–120 °C). On the other hand, cross-couplings with aryl chlorides have to date been performed also in ILs but (a) in the presence of phosphine ligands,[5i] (b) with the use of Pd nanoparticles stabilised by tetraalkylammonium salts bearing long alkyl chains,[5j] or (c) by employing hydroxyl-functionalised ILs.[5k] N-Methyliminodiacetic acid (MIDA) boronates, developed and largely used by Burke,[6] represent a more robust alternative to organoboranes to tackle the above-mentioned critical issues.[7] Alternative nucleophilic partners that, similarly to MIDA boronates, have proven largely superior to boronic acids and esters in terms of physicochemical properties, atom economy and scalability are potassium organotrifluoroborates. These compounds are free-flowing crystalline solids exhibiting excellent air and moisture stability, and easy storability.[8a–d] Applications in SM coupling of a wide range of (hetero)aryl-,[8e–h] alkenyl-,[8i,j] and alkynyl organotrifluoroborates[8k] have been developed.

Recent pioneering work from several synthetic laboratories worldwide has recognised the potential of the so-called 'Deep Eutectic Solvents' (DESs) (also known in the literature as Low-Melting Mixtures, LMMs) as superior green and bio-renewable solvents. DESs are today generally referred to as combinations of two or three safe and inexpensive components able to engage in reciprocal hydrogen-bond interactions to form a eutectic mixture with a melting point far below those of the

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individual components, due to self-association. They are usually formed by mixing and gently heating a quaternary ammonium salt (e.g., choline chloride, ChCl) and a neutral hydrogen-bond donor (HBD) [e.g., glycerol (Gly), urea, carbohydrates, carboxylic acids] in a specific molar ratio. DESs display attractive advantages, such low price, non-flammability, recyclability and low vapour pressure, and are believed to be more biodegradable and less toxic than traditional ionic liquids because of their environmentally friendly components.[9] The solvent properties can also be tuned by simply changing the nature and the molar ratio of the components.

The applications of DESs and other unconventional solvents in the fields of metal-catalysed[5g,10] and metal-mediated organic reactions,[11] have been experiencing an explosive growth and development, particularly in recent years. As for SM reactions, however, to the best of our knowledge, there are only two reports: (*i*) Köning and co-workers documented the use of LMMs based on sugar-urea-salt melts as solvents to promote Pd-catalysed couplings between phenylboronic acid and aryl bromides at 90 °C (Scheme 1a);[12a] (*ii*) Ramón, Alonso and co-workers successfully cross-coupled phenylboronic acid with both aryl bromides and iodides in a ChCl-based DES working with structurally engineered phosphine ligands and PdCl₂ at 100 °C (Scheme 1b).[12b]
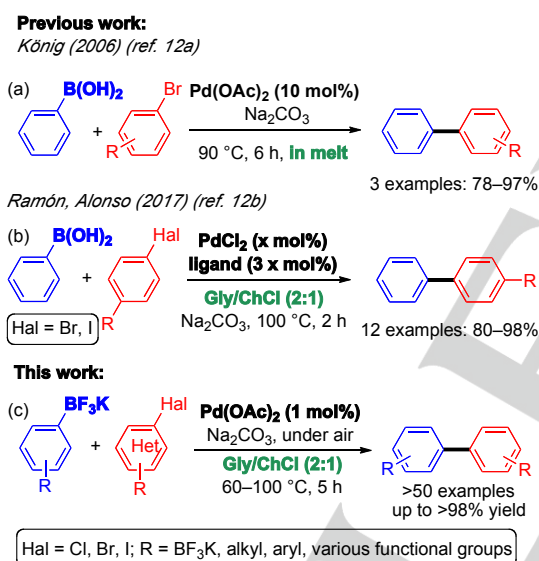


**Scheme 1.** (a) SM coupling in melt; (b) ligand-based SM coupling with PhB(OH)₂ in DES; (c) ligand-free SM coupling with ArBF₃K in DES.
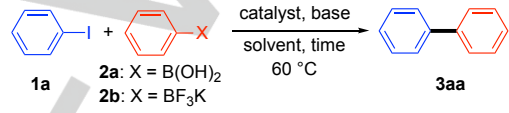
Our efforts of late have focused on using water and DESs to explore novel paradigms in organometallics,[10l,10p,11b–g,11j] organocatalysis,[13] biocatalysis,[14] solar technology[15a] and photosynthesis.[15b] Herein, we wish to report a systematic study on the usefulness of DESs as sustainable reaction media for ligand-free SM couplings between mono- and bifunctional potassium aryltrifluoroborates and (hetero)aryl halides (Scheme 1c). After extensive optimisation of the procedure, the Gly/ChCl (2:1) eutectic mixture proved to be the most effective for (a) assemblying symmetrical and non-symmetrical biaryl and, for the first time, also terphenyl

derivatives in good to excellent yields of up to and above 98%, *even starting from challenging aryl chlorides as organic electrophiles*, (b) using up to 1 mol% Pd(OAc)₂ as catalyst in the absence of any additional ligand, (c) running reactions under very mild reaction conditions; that is, under air and gently warming (60 °C for aryl bromides and iodides), and (d) efficient recycling of the DES, catalyst and base up to six times without appreciable loss of activity (E-factor: 8.74). Examples also include comparison with the performance of boronic acids as reaction partners under optimised reaction conditions.

## Results and Discussion

We set out to investigate the reaction between iodobenzene (**1a**) (0.5 mmol) and phenylboronic acid (**2a**) (2 equiv.) in different bio-based DESs and LMMs for the preparation of biphenyl (**3aa**) using Pd(OAc)₂ (10 mol%) as catalyst and Na₂CO₃ (2 equiv.) as base (Table 1).

**Table 1.** Optimisation of the SM coupling in DESs between iodobenzene (**1a**) and phenylboronic acid (**2a**) or phenyltrifluoroborate **2b**.[a]



| Entry | Solvent | Catalyst (mol%) | **2** (equiv.) | Time (h) | **3aa** yield (%)[b] |
|---|---|---|---|---|---|
| 1 | PG/ChCl[c] | Pd(OAc)₂ (10) | 2[d] | 24 | NR[e] |
| 2 | EG/ChCl[c] | Pd(OAc)₂ (10) | 2[d] | 24 | NR[e] |
| 3 | LA/ChCl[c] | Pd(OAc)₂ (10) | 2[d] | 24 | 52 |
| 4 | D-fructose/urea[c] | Pd(OAc)₂ (10) | 2[d] | 24 | 40 |
| 5 | urea/ChCl[c] | Pd(OAc)₂ (10) | 2[d] | 24 | 96 |
| 6 | Gly/ChCl[c] | Pd(OAc)₂ (10) | 2[d] | 24 | >98[f] |
| 7 | Gly/ChCl[c] | Pd(OAc)₂ (10) | 1[g] | 24 | 75 |
| 8 | Gly/ChCl[c] | Pd(OAc)₂ (10) | 1.5[h] | 24 | >98 |
| 9 | Gly/ChCl[c] | Pd(OAc)₂ (10) | 1.5[h] | 24 | 84[i] |
| 10 | Gly/ChCl[c] | PdCl₂ (10) | 1.5[h] | 24 | 80 |
| 11 | Gly/ChCl[c] | Pd(OAc)₂ (10) | 1.5[h] | 1 | 63 |
| 12 | Gly/ChCl[c] | Pd(OAc)₂ (10) | 1.5[h] | 5 | >98 |
| 13 | Gly/ChCl[c] | Pd(OAc)₂ (5) | 1.5[h] | 5 | >98 |
| 14 | Gly/ChCl[j] | Pd(OAc)₂ (5) | 1[g] | 5 | >98 |
| 15 | Gly/ChCl[j] | Pd(OAc)₂ (1) | 1[g] | 5 | >98 |

[a] Reaction conditions: 1.0 g DES per 0.5 mmol of **1a**; DES: propylene glycol (PG)/ChCl (3:1, mol mol⁻¹); ethylene glycol (EG)/ChCl (3:1, mol mol⁻¹); L-lactic acid (LA)/ChCl (2:1, mol mol⁻¹); D-fructose/urea (3:2, w/w); urea/ChCl (2:1, mol mol⁻¹); Gly/ChCl (2:1, mol mol⁻¹). [b] The yields reported are for products isolated and purified by column chromatography. [c] Substrate **2a**. [d] 2 Equiv. **2a** and Na₂CO₃. [e] NR = no reaction. [f] NR in the absence of Na₂CO₃ or when using Et₃N (2 equiv.). [g] 1 Equiv. **2a** (or **2b**) and Na₂CO₃. [h] 1.5 Equiv. **2a** and Na₂CO₃. [i] T = 25 °C. [j] Substrate **2b**.

When the above mixture was heated at 60 °C for 24 h in DESs formed between ChCl and ethylene glycol, propylene glycol or L-lactic acid, as well as in a D-fructose/urea LMM, unsatisfactory outcomes resulted, with yields of **3aa** of up to 52% (Table 1, entries 1–4). Upon changing the HBD to urea or Gly, **3aa** could be isolated in 96 or >98% yield, respectively (Table 1, entries 5,6). It was shown that in the absence of $Na_2CO_3$ or by replacing it with weaker bases such as $Et_3N$, no coupling took place (Table 1, entry 6). The amount of **2a** could also be reduced up to 1.5 equiv. without affecting the final yield (Table 1, entries 7,8), whereas the target product was formed in a lower yield by running the reaction at room temperature (r.t.) (Table 1, entry 9). Further screening of catalysts revealed that while $PdCl_2$ (10 mol%) gave a reaction yield of **3aa** of 80% (Table 1, entry 10),

other Pd salts [$Pd(PPh_3)_4$ (10 mol%), Pd/C (10 mol%)] as well as different salts of transition metals [CuI (10 mol%), $CuSO_4$ (10 mol%), $FeCl_2$ (10 mol%), $FeCl_3$ (10 mol%)] completely suppressed the formation of the cross-coupling product in the ChCl/Gly reaction medium. A reaction time of up to 5 h was also enough to recover **3aa** quantitatively (Table 1, entries 11,12). Finally, to further improve this procedure, we also reduced the catalyst loading, and were delighted to find that **3aa** still formed in quantitative yield with a loading of 5 mol%. (Table 1, entry 13). Notably, upon replacing **2a** with the corresponding potassium phenyltrifluoroborate **2b**, employed in a strict 1:1 stoichiometric ratio with **1a**, the effectiveness of such a cross-coupling was still maintained (**3aa**: >98% yield) either with 5 mol% $Pd(OAc)_2$ or with a loading as low as 1 mol% (Table 1, entries 14,15).

**Table 2.** Synthesis of biaryls **3** via SM coupling between (hetero)aryl halides **1** and arylboronic acids **2a**,**2f** or aryltrifluoroborates **2b–e** in eutectic mixture ChCl/Gly.[a]
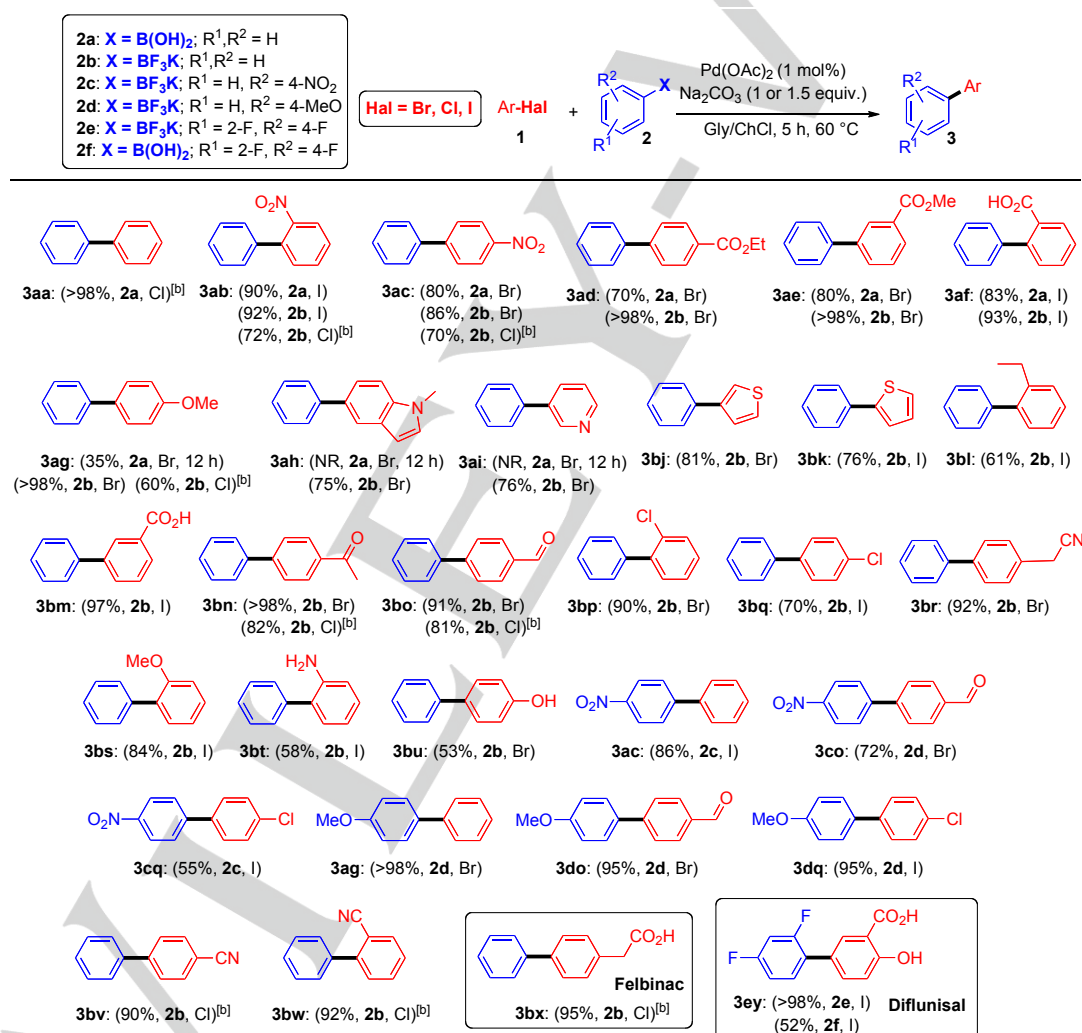


[a] Reaction conditions: (hetero)aryl halide (0.5 mmol), phenylboronic acid (**2a**,**2f**) (1.5 equiv.) or aryltrifluoroborate (**2b–e**) (1 equiv.), $Na_2CO_3$ (**2a**,**2f**: 1.5 equiv.; **2b–e**: 1 equiv.), DES (Gly/ChCl, 2:1) (1.0 g), in air. The yields reported are for products isolated and purified by column chromatography. NR = no reaction. [b] T = 100 °C.

With satisfactory conditions found, we sought to capitalise on this by exploring the scope of the reaction with a variety of (hetero)aryl halides (**1**) and arylboronic acids (**2a,2f**) (1.5 equiv.) or aryltrifluoroborates (**2b–e**) (1 equiv.) (Table 2). With regard to **2a**, the relatively higher yields (70–90%) of the desired coupled products (**3ab–3af**) were obtained when both aryl iodides and bromides bearing electron-withdrawing groups at the *ortho*-, *meta*- and *para*-positions, such as nitro, carboxylic acid and ester groups (**1b–f**), participated in the process (Table 2). However, the presence of an electron-donating group (MeO) at the *para* position (**1g**) dramatically hindered the coupling reaction with **1a**, and the expected product **3ag** formed in 35% yield only even after 12 h. Nitrogen heterocyclic substrates, such as 5-bromo-1-methylindole (**1h**) and 3-bromopyridine (**1i**), did not react either with **2a**, and thus the formation of products **3ah,3ai** did not occur (Table 2). Remarkably, upon switching to potassium phenyltrifluoroborate **2b** as the nucleophilic partner, the yield range of products **3ab–3ag** increased to 86–98%, and even bromo heterocycles **1h,i** could now be efficiently cross-coupled to give the desired adducts **3ah,3ai** in good yields (75–76%, Table 2). Using electron-rich five-membered heterocycles, such as 3-bromothiophene (**1j**) and 2-bromothiophene (**1k**), and assorted aryl derivatives with 'neutral' substituents (**1l**), or with electron-withdrawing (carboxylic, carbonyl, chloro, cyanomethyl) (**1m–r**) or electron-donating (MeO) (**1s**) groups, 61–98% yields of the expected products **3bj–3bs** were obtained (Table 2). Compounds **3bj** and **3bk** are important carbon scaffolds, since several thiophene derivatives are known for their electrochemical behaviour,[16] and are present in a variety of pharmaceutical compounds and natural products.[17] Aryl halides **1t,u**, with free amino and hydroxyl groups at the *ortho*- and *para*-positions, also participated in the coupling process with salt **2b** to afford biphenyl derivatives **3bt,3bu**, albeit in moderate yields (53–58%) (Table 2). Aryltrifluoroborates containing electron-deficient or electron-rich substituents (**2c,d**) proved to be competent nucleophilic partners as well, and by reaction with **1a** and with aryl bromides and iodides functionalised with a formyl (**1o**) or with a chloro (**1q**) group, delivered disubstituted biphenyls **3ac**, **3co**, **3cq**, **3ag**, **3do**, and **3dq** in 55–98% yield (Table 2).

In consideration of their commercial availability, we also made use of aryl chlorides for further investigation. Interestingly, it was uncovered that biphenyl **3aa** could be isolated in quantitative yield by simply heating the reaction mixture from 60 to 100 °C, without adding any additional ligand, and without increasing catalyst loading. Under these conditions, starting from 4-chloro- and 2-chlorobenzonitriles **1v** and **1w**, excellent yields were obtained for the corresponding biphenyl derivatives **3bv** and **3bw** (90–92%). 4-Acetyl-, 4-formyl-, 4-methoxy-, 2-nitro- and 4-nitrophenyl chlorides proved to be good performers as well, thereby giving rise to adducts **3ab**, **3ac**, **3ag**, **3bn**, and **3bo** in 70–82% yields (Table 2). Interestingly, using the combination of 2-(4-chlorophenyl)acetic acid (**1x**) and phenyltrifluoroborate **2b** or of 2-hydroxy-5-iodobenzoic acid (**1y**) and aryltrifluoroborate **2e** as coupling partners, we straightforwardly prepared in 96% and >98% yield, respectively, the analgesic, non-steroidal anti-inflammatory drugs Felbinac (**3bx**)[18] and

Diflunisal (**3ey**).[19] It is worh noting that **3ey** was prepared in a lower yield (52%) starting from arylboronic acid **2f** (Table 2).
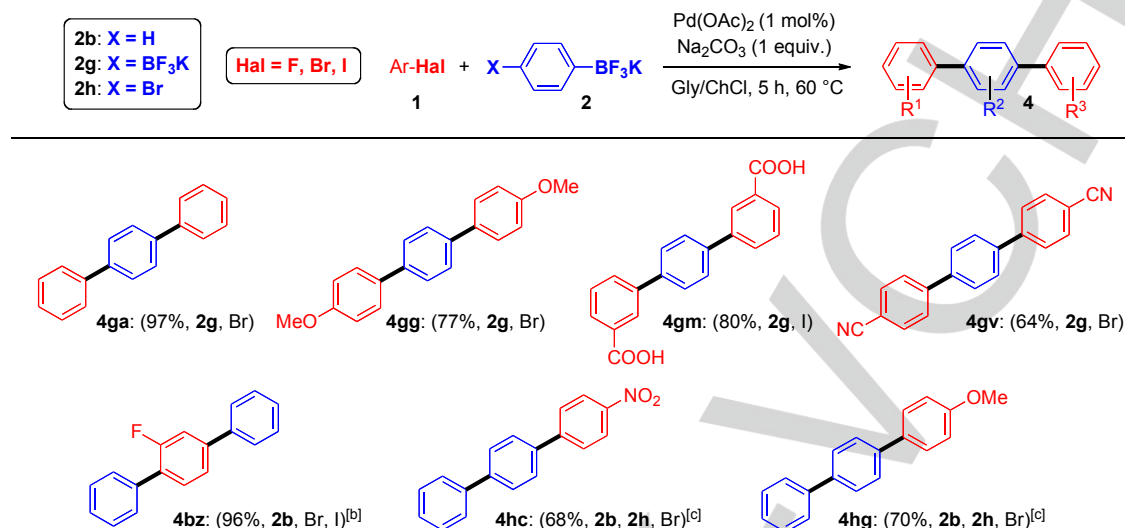
Some considerations are worth making at this point. As has been pointed out in the introduction, the side reactions that boronic acids are more susceptible to in SM coupling are dehydroboration, protodeboronation, oxidation, and Pd-catalysed homocoupling. Detailed mechanistic studies performed by Lloyd-Jones and co-workers have demonstrated that (a) organotrifluoroborates do not remain intact under basic, protic conditions, and that their complete hydrolysis to the corresponding boronic acids is a prerequisite for the transmetalation reaction to take place;[20] (b) the superior reaction outcome usually observed employing organotrifluoroborates originates not from a more rapid transmetalation step, rather from a suppression of side-product formation.[21] Thus, organotrifluoroborates serve as stable reservoirs for boronic acids, and the endogenous fluoride liberated from the hydrolysis jointly with the slow release and the low concentration of boronic acids formed from the potassium salts are all important features contributing to the attenuation of the above side reactions. This is also consistent with our findings. Indeed, in all investigated cases depicted in Table 2, the performance of aryltrifluoroborates proved to be always superior to that of the corresponding arylboronic acids. Now, the question is: if organotrifluoroborate hydrolysis is crucial for the transmetalation step, how can this take place in DESs? An important observation of our study is that no coupling occurs starting from completely anhydrous eutectic mixtures. Hydrophilic DESs have a tendency for water absorption closely dependent on the duration time of exposure in open air. A recent on-site quantitative Fourier transform infrared (FTIR) spectroscopic analysis performed by our group of residual water content in ChCl/Gly (1:2) eutectic mixture soon after its preparation was consistent with up to 2.2 wt% (1.6 M).[15b] Thus, most probably, the percentage of water incorporated in our hydrophilic DES once prepared in air may be playing a role in triggering the hydrolysis of organotrifluoroborates to the corresponding boronic acids.

To further explore the utility of this new protocol for Pd-catalysed cross-couplings using eutectic mixtures, we investigated the synthesis of functionalised terphenyl derivatives, which are interesting molecules displaying a variety of pharmaceutical and biological properties,[22] and are also essential for material science applications.[23] As shown in Table 3, we discovered that one-pot double SM cross-coupling reactions of bifunctional dipotassium phenylene-1,4-bis(trifluoroborate)[24] (**2g**) with **1a**, and with both electron-rich (**1g**) and electron-deficient (**1m,1v**) aryl bromides and iodides, proceeded uneventfully, thereby leading to conjugated symmetrical triaryl derivatives **4ga**, **4gg**, **4gm** and **4gv** in 64–97% yield. Of note, trihalogenated coupling module 1-bromo-2-fluoro-4-iodobenzene (**1z**) cross-coupled with good reaction efficiency as well as with **1b**, affording fluorinated terphenyl **4bz** in 96% yield (Table 3).[25] Lastly, the challenging one-pot three-component chemoselective assembly of two different aromatic moieties to give unsymmetrical terphenyl derivatives was also examined. Upon adding to a solution of *p*-bromonitrobenzene

(**1c**) or *p*-bromoanisole (**1g**) in Gly/ChCl (2.1), first, *p*-bromophenyltrifluoroborate **2h**, and then phenyltrifluoroborate **2b**, terphenyls **4hc** and **4hg** could be isolated in 68 and 70% yield, respectively (Table 3).

**Table 3.** Synthesis of terphenyls **4** via SM coupling between aryl halides **1** and aryltrifluoroborates **2b**,**2g**,**h** in eutectic mixture ChCl/Gly.[a]



4**ga**: (97%, **2g**, Br)    **4gg**: (77%, **2g**, Br)    **4gm**: (80%, **2g**, I)    **4gv**: (64%, **2g**, Br)

**4bz**: (96%, **2b**, Br, I)[b]    **4hc**: (68%, **2b**, **2h**, Br)[c]    **4hg**: (70%, **2b**, **2h**, Br)[c]

[a] Reaction conditions: aryl halide (**1**) (0.5 mmol; 1.0 or 2.0 equiv.), aryltrifluoroborate (**2b**,**2g**,**h**) (1.0 equiv.) DES (Gly/ChCl, 2:1) (1.0 g), in air. The yields reported are for products isolated and purified by column chromatography. [b] Phenyltrifluoroborate **2b** (2.0 equiv.) was cross-coupled with 1-bromo-2-fluoro-4-iodobenzene (**1z**). [c] Both phenyltrifluoroborate **2b** (1.0 equiv.) and *p*-bromophenyltrifluoroborate **2h** were cross-coupled with *p*-bromonitrobenzene (**1c**) or with *p*-bromoanisole (**1g**) (see main text).

The recycling of the catalyst was also realised by exploiting the different solubility properties that Pd(OAc)$_2$ proved to exhibit in the DES employed and in other organic solvents. The reference conditions were those set up for the reaction between **1a** (1.0 mmol) and **2b** (1.0 equiv.) in 1.0 g DES and with 5 mol% Pd(OAc)$_2$ (Table 1, entry 14). Once the stirring was stopped after 5 h reaction time, and the reaction mixture was washed with 1 mL cyclopentyl methyl ether (CPME),[26] product **3aa** could be recovered quantitatively (>98% yield) leaving the catalyst in the eutectic mixture.[27]

Then, upon simply adding new, fresh reagents, the catalyst (jointly with DES and base) could be successfully re-used for further reaction runs. The catalyst remained active over six cycles with a decrease in the final yield of **3aa** up to 8%: 98% (second run), 95% (third and fourth run), 94% (fifth run), and 92% (sixth run). (Figure 1a). Pd(OAc)$_2$ is employed as a heterogeneous catalyst precursor.[27] In ligandless SM coupling, it is usually reduced *in situ* to form catalytically active Pd(0) nanoparticles (NPs) whose nucleation is especially hard to control kinetically.[28] Indeed, because of their high surface energy, PdNPs tend to aggregate with each other into larger particles. This often results in a marked reduction of their catalytic activity, eventually leading to the deposition of Pd black. A black precipitation of palladium was also observed during our reactions. This might explain the progressive decrease of activity detected during the recycling of the catalyst. However, the fact that a good catalytic activity is still detected after 6 runs

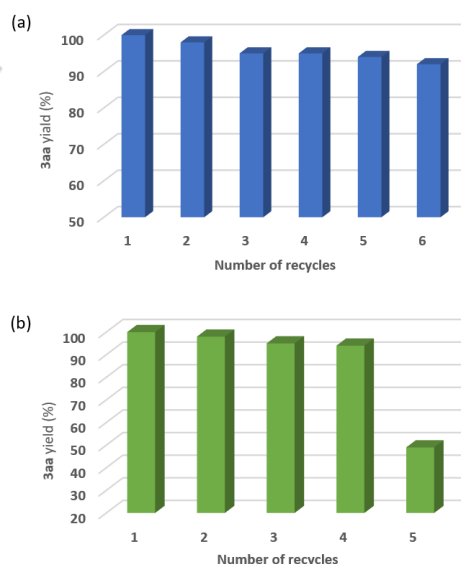suggests a possible stabilising role played by DES components (e.g., choline chloride) on the above PdNPs.[29]



**Figure 1.** Recycling of Pd(OAc)$_2$, DES and Na$_2$CO$_3$ in the coupling reaction between iodobenzene (**1a**) and phenyltrifluoroborate (**2b**) with (a) 5 mol%, or (b) 1 mol% catalyst.

On the other hand, the recycling efficiency proved to be lower when using 1 mol% Pd(OAc)$_2$. In this case, the catalyst

remained well active and could be efficiently recycled only over four cycles (**3aa**: >98% yield first run; 94% yield fourth run) (Figure 1b). The chemical yield of **3aa** significantly dropped down to 49% in the fifth and up to 46% yield in the sixth cycle most probably because of the additional loss of palladium during the work-up process. Indeed, we have experimentally ascertained that no coupling occurs with a catalyst loading of down to 0.1 mol%. The associated E-factors[30] for the two recycling processes were 8.74 (5 mol% catalyst, 6 cycles) and 9.25 (1 mol% catalyst, 4 cycles) (see ESI for details).[31]

## Conclusions

In summary, the environmentally friendly eutectic mixture ChCl/Gly (1:2) turned out to be the most effective reaction medium for carrying out Suzuki–Miyaura couplings involving mono- and bifunctional aryltrifluoroborates as nucleophilic partners in the absence of additional ligands, and using to up to 1 mol% Pd(OAc)$_2$ as catalyst, Na$_2$CO$_3$ as base, and an efficient recycling sequence of catalyst, base and DES with an E-factor as low as 8.74. The presented protocol can be run in air and under gentle heating for (hetero)aryl bromides and iodides (60 °C), and tolerates many functional groups such as nitro, cyano, carboxylic acids, esters, halides, carbonyl derivatives, alkoxy and free hydroxy and amino functionalities. Valuable biaryl and terphenyl derivatives (more than 50 cases compared and discussed), which play a pivotal role in the pharmaceutical industry, materials science and catalysis, have been successfully synthesised in yields of up to and above 98%, also starting from challenging aryl chlorides, by simply increasing the temperature to 100 °C. The methodology was applied to the synthesis of the non-steroidal anti-inflammatory drugs Felbinac and Diflunisal. Efforts towards reshaping other traditional cross-coupling methods employing sustainable, nonconventional solvents are underway and will be reported in due course.

## Experimental Section

**General procedure for Pd-catalysed Suzuki-Miyaura reactions for the synthesis of biaryls 3 using aryltrifluoborates 2b–e or arylboronic acids 2a,2f and (hetero)aryl halides in Gly/ChCl.**

To a suspension of potassium aryltrifluoborate (**2b–e**) (0.5 mmol) [for arylboronic acids **2a,2f**: 0.75 mmol] in 1.0 g of Gly/ChCl (2:1 mol mol$^{-1}$), (hetero)aryl halide (**1a–y**) (0.5 mmol), Na$_2$CO$_3$ (53 mg, 0.5 mmol), and Pd(OAc)$_2$ (1.1 mg, 0.005 mmol) were sequentially added. The reaction mixture was stirred at 60 ºC (aryl chlorides: 100 °C) in air for 5 h until complete consumption of the starting material (monitored by TLC), then cooled to room temperature, and finally extracted with 1 mL of CPME. The organic layer was filtered through a Celite pack and evaporated under reduced pressure to afford the crude product. The latter was purified by column chromatography on silica gel (hexane/EtOAc 5:1 ÷ 4:1) to provide the desired biaryl **3** (see Table 2).

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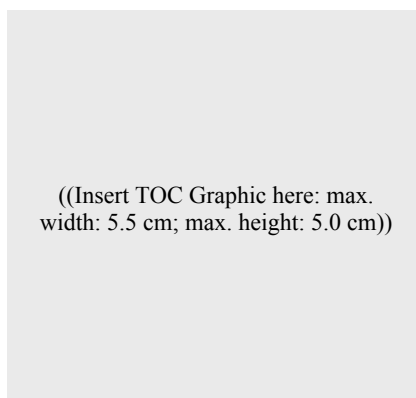
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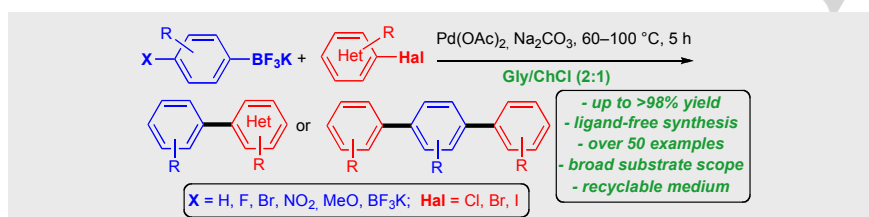
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