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Pd-Catalyzed Suzuki-Miyaura Cross-Coupling Reaction in Glycerol Using KOH as Base and Glycerol-Triethanolamine Deep Eutectic Solvent under Inorganic Base-Free Conditions

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Glycerol and glycerol-triethanolamine deep eutectic solvent are both environmentally benign, cost-effective, and practical solvents for the Pd-catalyzed Suzuki-Miyaura cross-coupling of aryl halides with arylboronic acids. Utilizing KOH as base, the reaction in glycerol proceeded smoothly with low catalyst loadings (up to 0.5 mol% of $PdCl_2(PPh_3)_2$) providing excellent yields (up to 99%) of the cross-coupling products, which can be readily extracted with hexane. However, the recyclability of the glycerol medium containing the catalyst is limited to a few cycles. Furthermore, it was explored the use of chlorodiphenylphosphine as a pre-ligand. Although glycerol phosphinite was not generated *in situ*, PPh_2Cl proved to be an excellent pre-ligand, yielding the coupling product with a 98% yield. Compared to glycerol, glycerol-triethanolamine deep eutectic solvent (TEOA:G DES) proves to be a superior solvent for the cross-coupling reaction. In addition, the presence of amine group in the solvent allowed to obtain an inorganic base-free cross-coupling protocol. Aryl bromides and aryl boronic acids containing both electron releasing and attracting functional groups can be coupled without requiring the addition of any further base, affording the biphenyl products in moderate to good yields. The cross-coupling products can be easily isolated by extraction with hexane. Moreover, we observed the formation of triethanolamine phenylboronate during the reaction. The triethanolamine boronate was subsequently synthesized through the condensation of phenylboronic acid with triethanolamine and fully characterized. ^{11}B nuclear magnetic resonance (NMR) spectroscopy confirmed the coordination of the nitrogen to the boron atom of the triethanolamine boronate.

Keywords: Suzuki-Miyaura, cross-coupling, base-free, glycerol, triethanolamine, deep eutectic solvent

Introduction

Palladium-catalyzed Suzuki-Miyaura cross-coupling reactions are the most powerful and versatile protocols for the construction of Csp^2–Csp^2 bonds because they are simple, cost-effective, and display a tolerance for a variety of functional groups under mild-conditions.[1,2] This cross-coupling methodology rapidly became widely used in organic synthesis and material science, and had a very strong impact on the pharmaceutical, agrochemical, and fine chemical industries.[3] However, as for any homogeneous organometallic catalyzed reaction, the increasing environmental challenges and the difficulty of separating the desired products from the reaction mixture have restricted its synthetic utility to some extent because the majority of waste generated *per* gram of the product includes the solvent waste,[4] in addition to the inorganic salts and the byproducts from the cross-coupling reactions. Considering the impact of these chemical processes on the environment, and the cost of the organic solvents, the search for innovative procedures for the substitution of volatile and expensive organic solvents has become a big challenge in both academia and industry.[5] Therefore, the search for environmentally benign reaction media has remained an important issue for the Pd-catalyzed Suzuki-Miyaura cross-coupling reactions.[6]

In this context, glycerol provides an attractive alternative, since it offers the desired characteristics of a green solvent including low flammability, high availability, biodegradability, eco- friendliness, and it can be obtained from renewable sources.[7] With increased

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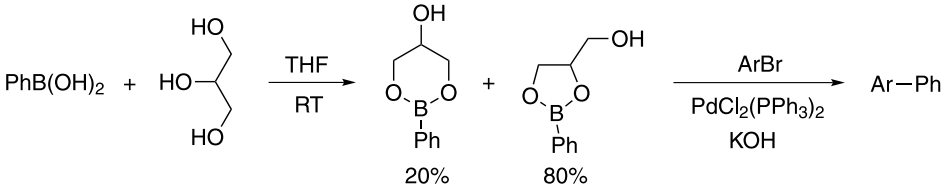
worldwide biodiesel production, the market saturation of glycerol, a co-product of biodiesel production (for every 9 kg of biodiesel produced, about 1 kg of a crude glycerol co-product is formed), is inevitable, especially in Brazil.[8,9] Glycerol derivatives, such as glycerol carbonate, have been used as green solvents in industrial applications as glycerol derivatives.[10] Glycerol has been extensively explored as a green solvent in homogeneous and heterogenous catalytic reactions, despite its high viscosity at ambient temperatures and the low solubility of highly hydrophobic reagents.[11] The Pd-catalyzed Suzuki-Miyaura cross-coupling reaction in glycerol was first studied by reacting phenyl iodide or phenyl bromide and phenyl boronic acid as coupling partners and very good yields were obtained by using Pd complexes containing water-soluble triphenylphosphine trisulfonate (TPPS) as catalysts.[12] Glycerol has been also evaluated as a solvent for microwave and ultrasound irradiation procedures,[13] including the Suzuki-Miyaura coupling reaction.[12,14,15]

Deep eutectic solvents (DESs) have been used as alternative green and sustainable media in many chemical processes, including some reports in Pd-catalyzed cross-coupling reactions.[16,17] For instance, DES choline chloride/glycerol (1:2) has been used as a medium in ligand-free Suzuki-Miayura cross-coupling using aryltrifluoroborates as coupling partners.[18] Another DES formulation, consisting of potassium carbonate and ethylene glycol, has served as solvent in both Pd-catalyzed Suzuki-Miyaura and Sonogashira reactions.[17] Remarkably, given potassium carbonate's effectiveness as base in cross-coupling reactions, there was no need for additional bases to achieve good yields of the coupling products. Triethanolamine, in conjunction with glycerol, has recently found utility as a deep eutectic solvent, having been used for seed oil extraction and cosolvent in biodiesel production.[19,20] A deep eutectic solvent composed of glycerol and triethanolamine would be an excellent and eco-friendly solvent for cross-coupling process. In fact, triethanolamine is a biodegradable compound commonly employed in cosmetics, pharmaceuticals, and other industries.[21] Furthermore, there is a potential for Suzuki-Miyaura cross-coupling process if the amine moiety can function as base. When triethanolamine was used as base (at 2 equivalents), only traces of coupling product were observed in the cross-coupling of phenylboronic acid with 1-bromo-4-methylbenzene using Pd@Al_2O_3-agarose as the catalyst.[22] However, when triethanolamine was used as solvent, the Pd-catalyzed Heck reactions involving aryl bromides and iodides proceeded to furnish the corresponding products in good to excellent yields without the need for additional additives.[23]

In our ongoing project focusing on Pd-catalyzed cross-coupling reactions, glycerol was used in the synthesis of glycerol phenylboronates, which were subsequently employed in Pd-catalyzed Suzuki cross-coupling reactions. Specifically, the reaction of glycerol with phenylboronic acid resulted in a mixture of glycerol 1,2-phenylboronate and 1,3-phenylboronate (Scheme 1).[24] Typically, arylboronic acids are used in excess (1.5-2.0 equivalents) to ensure complete conversion of aryl halides. Interestingly, only 1.05 equivalents of glycerol phenylboronates were necessary to obtain the products in high yields. Consequently, in addition to the advantages previously outlined, the use of glycerol as a solvent could eliminate the need for excess boronic acid in Suzuki-Miyaura reactions. Furthermore, we explored the potential for phosphorus-based ligands to react with glycerol, thereby enhancing the immobilization of the catalyst within the glycerol medium. In this context, we first present the scope of the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction between aryl bromides and arylboronic acids in glycerol, along with an assessment of the recyclability of the catalytic system. Subsequently, we introduce the Pd-catalyzed Suzuki-Miyaura cross-coupling in a DES comprising triethanolamine and glycerol under inorganic base-free conditions. Additionally, triethanolamine boronate esters, that were formed *in situ*, were subsequently synthesized, and characterized for the first time.

Experimental

All reactions were carried out in an argon atmosphere in resealable Schlenk tubes. All chemicals were purchased from commercial sources (Sigma-Aldrich Merck, Germany) and used without further purification. Glycerol was degassed by purging a layer of argon for 15 to 20 min before its use in a reaction. Nuclear magnetic resonance (NMR) spectra were recorded with a Varian 400 spectrometer and



Scheme 1. Phenylboronic esters from glycerol as active coupling partners for the Suzuki-Miayura cross-coupling reaction.

a Bruker Avance 400 MHz. Mass spectra were obtained on a gas chromatograph-mass spectrometer (GC-MS) Shimadzu QP-2010 SE (EI, 70 eV) equipped with a 30 m DB-17MS column. Gas chromatography analyses were performed on a Shimadzu GC-2010 Plus equipped with a 30 m DB-17 column and flame ionization detector (FID) detector. The infrared (IR) spectra were obtained using attenuated total reflectance (ATR) technique, on a Bruker Alpha-*P* spectrometer. The high-resolution mass spectrometer (HRMS) data were obtained on a Bruker ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometer (UHPLC-QTOF-MS) instrument, operating on positive mode.

Preparation of triethanolamine:glycerol deep eutectic solvent (TEOA:G DES)[19]

Triethanolamine (62.4 g, 42 mmol) was mixed with glycerol (77.0 g, 84 mmol) in a Schlenk flask. The flask was evacuated, back-filled with argon, and stirred at 100 ºC for 4 h. A homogenous pale-yellow liquid was formed and stored under argon.

Synthesis of arylboronic triethanolamine esters

Arylboronic triethanolamine esters were obtained by adapted procedure used in our laboratory for the synthesis of arylboronic glycerol esters.[24] Then, triethanolamine was added to a solution of arylboronic acid in 20 mL of tetrahydrofuran (THF) at room temperature, and the mixture was stirred overnight. The solvent was evaporated under reduced pressure and the product was washed with small portion of ether and dried.

Triethanolamine phenylboronate (**1**)

Using 654.8 mg (4.4 mmol) of triethanolamine, and 534.7 mg (4.4 mmol) of phenylboronic acid, a viscous oil was obtained (800 mg, 77%). IR (ATR) ν / cm^{-1} 3322 (br), 3032, 2955, 2931, 2873, 1597, 1503, 1210, 1063, 997, 944, 925, 830, 819, 719; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H), 7.27-7.24 (m, 3H), 3.97 (t, *J* 6.1 Hz, 4 H), 3.82 (s br, 1 H), 3.60 (s br, 2 H), 3.10-2.90 (m, 4 H), 2.35 (t, *J* 5.1 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 127.7, 127.4, 63.0, 60.7, 58.0, 57.3; ^{11}B NMR (128.4 MHz, $CDCl_3$) δ 12.9; HRMS-(+) *m/z*, calcd. for $C_{12}H_{19}BNO_3$ $[M + H]^+$: 236.1453, found: 236.1456.

Triethanolamine 4-methoxyphenylboronate (**2**)

Using 430 mg (2.88 mmol) of triethanolamine, and 437 mg (2.87 mmol) of 4-methoxyphenylboronic acid, a white solid was obtained (533 mg, 70%). mp 164 ºC; IR (ATR) ν / cm^{-1} 3324 (br), 3031, 2956, 2930, 2873, 1597, 1504, 1211, 1180, 1168, 1065, 997, 943, 952, 925, 819, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* 8.3 Hz, 2 H), 6.80 (d, *J* 8.4 Hz, 2H), 3.97 (t, *J* 5.9 Hz, 4H), 3.78 (s, 3H), 3.69 (s br, 1 H), 3.61 (s br, 2), 2.99 (s br, 4H), 2.35 (t, *J* 5.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 134,5, 112,9, 62.9, 60,7 58.0, 57.2, 54.9; ^{11}B NMR (128.4 MHz, $CDCl_3$) δ 13.1; HRMS-(+) *m/z*, calcd. for $C_{13}H_{21}BNO_4$ $[M + H]^+$: 266.1558, found: 266.1560.

General procedure for the Suzuki-Miyaura cross-coupling reaction

For a typical Suzuki-Miyaura experiment, an oven-dried resealable Schlenk flask with a capacity of 10 mL was evacuated, back-filled with argon, and charged with a Pd complex (0.50-2.0 mol%) and phosphine ligand when noted (phosphine:Pd = 2:1), followed by the addition of aryl bromide (0.5 mmol), arylboronic acid (0.55 mmol), potassium hydroxide (KOH; 1.0 mmol, 56 mg), and glycerol (4.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Then, the solution was cooled to room temperature and extracted three times with a glycerol-immiscible solvent, in this case, hexane. The hexane phase was separated, dried over $MgSO_4$, and concentrated under vacuum. For the reactions obtained as mixtures, the desired products were then purified using silica gel flash chromatography eluting hexane only. The spectral data of the obtained cross-coupling products were in agreement with those described in the literature (see Supplementary Information (SI) section). Similar procedure was used for the reaction in TEOA:G DES and triethanolamine that were heated at 50 ºC before addition to the flask.

Suzuki-Miyaura cross-coupling reactions using PPh_2Cl and 2-(diphenylphosphino)benzaldehyde

PPh_2Cl (2.0 mol%) or 2-(diphenylphosphino) benzaldehyde (2.0 mol%) and the glycerol (4.0 mL) were directly mixed into an oven-dried resealable Schlenk tube which had been evacuated and back filled with argon; the cross-coupling reaction was then started and the mixture was magnetically stirred for 1 h at room temperature. Then, the general procedure for the Suzuki-Miyaura cross-coupling reactions was followed.

General procedure for the recycling experiments

For the recycling experiment, an oven-dried resealable Schlenk flask was evacuated and refilled with argon and charged with $PdCl_2(PPh_3)_2$ (2.0 mol%). Aryl bromide (0.50 mmol),

followed by arylboronic acid (0.55 mmol), and KOH (1.0 mmol, 56 mg), were then added to glycerol (4.0 mL) or a 1:1 mixture of glycerol and methanol (4.0 mL). The Schlenk tube was then sealed, and the reaction mixture was prompted during magnetic stirring at 80 °C for eight hours. Following five extractions with hexane, the resulting glycerol- and methanol-based catalytic medium was evacuated and backfilled with argon three times to ensure an oxygen-free catalytic medium, which was then reused for the next reaction. Then, equal amounts of aryl bromide (0.50 mmol), arylboronic acid (0.55 mmol), and KOH (1.0 mmol, 56 mg) were added, and the reaction was stirred overnight (16 h). Thus, alternative 8- and 16-h cycles, i.e., two cycles *per* day were performed over up to eight cycles.

Results and Discussion

Suzuki-Miyaura cross-coupling reaction in glycerol

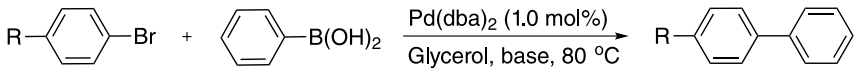
For a typical Suzuki-Miyaura cross-coupling reaction, phenyl bromide and 4-bromotoluene were used as model substrates to react with phenylboronic acid. To decrease the viscosity of glycerol, the reactions were carried out at 80 ºC. Initially, we investigated the reaction of aryl bromides with phenylboronic acid using the zero valent ligand-free $Pd(dba)_2$ (dba: dibenzylideneacetone) as a catalyst precursor (Table 1). Thus, the reaction with 1.0 mol% of catalyst loading was magnetically stirred for four hours in the presence of various bases in 4.0 mL of glycerol under an inert atmosphere. Although ligand-free $Pd(dba)_2$ displayed activity in the coupling reaction, moderate yields (46-54%) were achieved with all bases after 4 h (Table 1, entries 1-4). Specifically, employing KOH as the base resulted in a 70% yield when the reaction was extended to 24 h (Table 1, entry 5).

The ligand-free $Pd(dba)_2$ was then compared with other phosphine-free and phosphine-based Pd complexes using KOH as base (Table 2). A lower yield (62%) was obtained using the ligand-free palladium acetate, $Pd(OAc)_2$ (Table 2, entry 2). For the evaluated Pd(II) complexes bearing phosphine ligands, an 81% yield of the cross-coupling product was obtained using $PdCl_2(PCy_3)_2$ (PCy_3: tricyclohexylphosphine) while a 99% yield was obtained using $PdCl_2(PPh_3)_2$ (Ph: phenyl) (Table 2, entries 3 and 4). It is important to mention that the coupling product was easily isolated by simply extracting the reaction mixture with a glycerol-immiscible solvent such as hexane. Wolfson and Dlugy[12] have reported that $PdCl_2$(dppf) (dppf: 1,1-bis(diphenylphosphino)ferrocene) gave the best results for the coupling of iodobenzene with phenylboronic acids, with no change of activity for three cycles (82, 80, and 80% yield). In order to compare the results, the model reaction was performed under similar conditions, i.e., using 2 mol% of $PdCl_2$(dppf), and a 76% yield was obtained after four hours (Table 2, entry 5). When the reaction was allowed to progress over 24 h of magnetic stirring, an 86% yield was obtained (Table 2, entry 6).

Under basic conditions, glycerol could react with 2-(diphenylphosphino)benzaldehyde leading to a hemi-acetal, improving the solubility of the catalyst in the glycerol phase and would subsequently offer a more efficient means for catalyst recycling. However, the catalytic system based on $Pd(OAc)_2$ and 2-(diphenylphosphino)benzaldehyde gave only a moderate yield of the cross-coupling product (Table 2, entry 7). Therefore, we decided not to evaluate the recyclability of this catalytic system.

Chlorodiphenylphosphine is widely used in the synthesis of various aryls- and alkydiphenylphosphines by reacting with aryl or alky Grignard reagents, respectively.[25] It has also been used as a cross-coupling partner in reactions with aryl bromides to generate functionalized triarylphosphines.[26] The P–Cl bond is reactive with many nucleophiles such as alcohol, generating the corresponding phosphinites (Ph_2POR) that are used as ligands in catalytic reactions, including Suzuki cross-coupling reactions.[27,28] The alkoxycarbonylation of (hetero)aryl bromides is developed in the presence of *in situ* generated

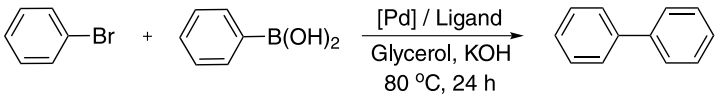
Table 1. Ligand-free $Pd(dba)_2$ catalyzed Suzuki-Miyaura reaction in glycerol[a]



entry	R	Base	time / h	Yield[b] / %
1	Me	K_3PO_4	4	50
2	Me	Na_2CO_3	4	54
3	Me	KOH	4	54
4	H	KOH	4	46
5	H	KOH	24	70

[a]Reaction conditions: 1.0 mol% $Pd(dba)_2$, 0.50 mmol aryl bromide, 0.55 mmol phenylboronic acid, 1.0 mmol base, 4.0 mL glycerol, 80 °C. [b]Isolated yield.

Table 2. Screening of Pd sources for the Pd-catalyzed Suzuki-Miyaura reaction in glycerol[a]

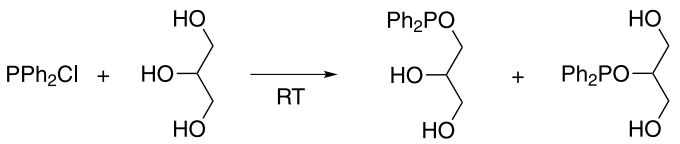


entry	[Pd] / mol%	Ligand / mol%	Yield[b] / %
1	$Pd(dba)_2$ (1)	–	70
2	$Pd(OAc)_2$ (1)	–	62
3	$PdCl_2(PCy_3)_2$ (1)	–	81
4	$PdCl_2(PPh_3)_2$ (1)	–	99
5	$PdCl_2$(dppf) (2)	–	76[c]
6	$PdCl_2$(dppf) (2)	–	86
7	$Pd(OAc)_2$ (1)	PPh_2(*o*-C_6H_4CHO) (2)	68
8	$Pd(OAc)_2$ (2)	PPh_2Cl (4)	98

[a]Reaction conditions: 0.50 mmol of aryl bromide, 0.55 mmol of phenylboronic acid, 1.0 mmol of KOH, 4.0 mL of glycerol, 80 °C, 24 h. [b]Isolated yield. [c]4 h. dba: dibenzylideneacetone; Ac: acetate; PCy_3: tricyclohexylphosphine; Ph: phenyl; dppf: 1,1-bis(diphenylphosphino)ferrocene.

phosphinite ligands tBu$_2$POR (R = nBu, nPr, Et or Me) was achieved using tBu$_2$PCl as the pre-ligand in the presence of different alcohols.[29] We expected that the treatment of PPh_2Cl with glycerol would form an *in situ* phosphinite ligand with two free hydroxyl groups, improving the solubility of the catalyst in the glycerol phase and subsequently allowing a more efficient recycling of the catalyst (Scheme 2).

The coupling product was obtained with a 98% yield using PPh_2Cl as pre-ligand (Table 2, entry 7). Therefore, the *in situ* glycerol phosphinite ligand formation was investigated by ^{31}P NMR using three different conditions after one hour of reaction at 80 ºC: (*i*) PPh_2Cl and KOH in glycerol; (*ii*) PPh_2Cl, KOH, and $Pd(OAc)_2$ in glycerol; (*iii*) cross-coupling reaction conditions. The ^{31}P NMR analysis of PPh_2Cl in $CDCl_3$ only displayed the expected signal at 81.8 ppm (see SI section).[30] On the other hand, the chemical shift expected for diphenylphosphinites ranged between 100 and 120 ppm. For instance, PPh_2OMe[31] and PPh_2OEt[26,32] have chemical shifts of 115.9 and 109.9 ppm, respectively. However, no phosphinite formation was observed during the reaction of PPh_2Cl and glycerol in the presence of KOH as a base (Figure 1a). The ^{31}P[^{1}H] NMR analysis showed that PPh_2Cl was completely consumed, and new signals were observed; two more intense signals at 25.6 and 21.9 ppm, and one less intense at –40.9 ppm. The ^{31}P NMR analysis also revealed that the signals at 21.9 and –40.9 ppm could be unequivocally assigned to diphenylphosphine oxide ($Ph_2P(O)H$, $^1J_{PH}$ 482 Hz) and diphenylphosphine (Ph_2PH, $^1J_{PH}$ 223 Hz), respectively (Figure S4, SI section).[33,34] The hydrolysis of chlorodiphenylphosphine produced the diphenylphosphine oxide,[35] and the formation of diphenylphosphine oxide could be rationalized by the reaction of chlorodiphenylphosphine with KOH generating the unstable diphenylphosphinous acid (Ph_2POH) which tautomerized to the stable diphenylphosphine oxide [$Ph_2P(O)H$].[36,37] Secondary diphenylphosphine could be obtained through the reduction of chlorodiphenylphosphine[38] or diphenylphosphine oxide,[39] and under our conditions, glycerol acted as a potential reducing agent under high temperature and basic conditions. We propose that the signal at 25.6 ppm could be assigned to the diphenylphosphinic acid [$Ph_2P(O)OH$]. In fact, it has been reported that the reaction of diphenylphosphine oxide with hydroxide ions can generate diphenylphosphinic acid [$Ph_2P(O)OH$].[40] On the other hand, the ^{31}P NMR chemical shift of the diphenylphosphinic acid ranged from 23.4 to 33.8 ppm as a singlet in the ^{31}P NMR analysis.[41-45] Diphenylphosphine oxide and diphenylphosphinic acid were also observed when $Pd(OAc)_2$ was added into the mixture with PPh_2Cl and KOH in glycerol (Figure 1b). The ^{31}P[^{1}H] NMR analysis of the catalytic reaction after one hour showed a much more complex set of signals (Figure 1c). Diphenylphosphine oxide was represented by the more intense peak, and the signal of diphenylphosphinic acid was weak. We



Scheme 2. Expected reaction of PPh_2Cl with glycerol.

propose that the signals at 33.8 and 35.6 ppm may have been related to the diphenylphosphinate glycerol esters $Ph_2P(O)OCH_2CH(OH)CH_2OH$ and $Ph_2P(O)OCH(CH_2OH)_2$ which can form from the reaction of diphenylphosphinic acid with glycerol. For instance, diphenylphosphinate methyl ester ($Ph_2P(O)OMe$) and ethyl ester ($Ph_2P(O)OEt$) display chemical shifts at 34.3 and 31.4 ppm, respectively.[46] We were unable to identify the other signals. However, we cannot rule out that some of the new signals may have been linked to phosphorus species coordinated to the Pd center. Although we were unable to obtain glycerol phosphinites, chlorodiphenylphosphine was an excellent pre-ligand, providing the coupling product with a 98% yield.

Since $PdCl_2(PPh_3)_2$ yielded the best results, this catalyst precursor was chosen to study the scope of the reaction in full details. With the best conditions in hand, we then explored the use of a variety of aryl bromides containing both electron releasing and attracting functional groups with different arylboronic acids to demonstrate the versatility of this protocol (Table 3). Two different Pd loadings (0.50 and 1.0 mol%) and reaction times (4 and 24 h) were evaluated, and moderate to excellent yields were obtained suggesting the tolerance of the catalytic system in glycerol for a variety of functional groups.

Arylboronic acids containing chloro groups as a substituent at *para* position were efficiently coupled without influencing the yield of the desired cross-coupling products (Table 3, entries 6, 18-20), suggesting that the glycerol-based Pd catalytic system was inactive for the Suzuki-Miyaura cross-coupling of aryl chlorides or that the produced chloride-substituted biaryl product was much less reactive than the aryl bromide. Indeed, no coupling reaction was observed when 4-chloroanisole, an aryl chloride with an electron donating group at *para* position, was used (Table 3, entry 21). However, the electron withdrawing group containing aryl chlorides at *para* position provided the cross-coupling product in a moderate yield (Table 3, entry 22).

Finally, the recyclability of the glycerol catalytic media recycling was investigated under optimized conditions. Following the extraction of the biaryl product from the first reaction using hexane several times (five times), the catalytic glycerol medium was dried under vacuum. Then, identical amounts of bromobenzene, phenylboronic acid, and KOH were added to the glycerol and the reaction was carried out under similar conditions. The results of the recycling catalytic glycerol media experiments are summarized in Table 4. The recycling studies were started using 2.0 mol% of $PdCl_2(PPh_3)_2$ that provided a quantitative yield of the cross-coupling product for the first run. However, a sharp decrease in the yield of the cross-coupling in the fifth cycle prevented the further recycling of the catalytic media. It has been reported that in the presence of $PdCl_2$(dppf) (2.0 mol%), the reaction between iodobenzene and phenyl boronic acid in glycerol could maintain the catalytic activity for three cycles.[12] However, we did not observe a similar behavior for the coupling with bromobenzene, and the yield dropped to only 28% for the second cycle. We then decided

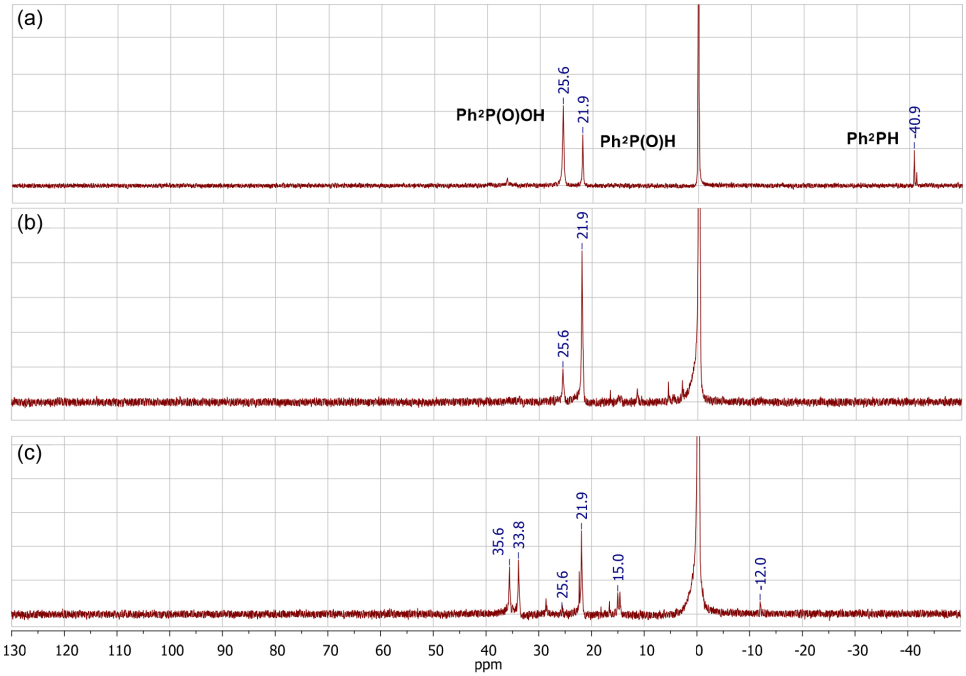
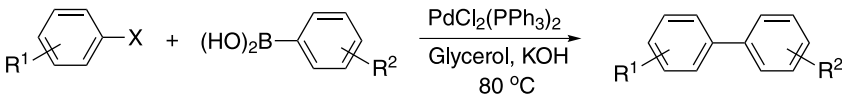


Figure 1. $^{31}P[^1H]$ NMR analysis after one hour of reaction at 80 ºC: (a) PPh_2Cl and KOH in glycerol; (b) PPh_2Cl, KOH, and $Pd(OAc)_2$ in glycerol; (c) cross-coupling reaction conditions.

Table 3. Substrate scope for the Suzuki-Miyaura reaction using $PdCl_2(PPh_3)_2$ in glycerol[a]



entry	X	R^1	R^2	$PdCl_2(PPh_3)_2$ / mol%	time / h	Yield[b] / %
1	Br	H	*p*-CF_3	0.50	4	54
2	Br	H	*p*-CF_3	0.50	24	79
3	Br	H	*p*-CF_3	1.0	24	99
4	Br	H	*p*-OBu	0.50	24	99
5	Br	H	*p*-F	0.50	24	97
6	Br	H	*p*-Cl	0.50	24	99
7	Br	H	*o*-Me	0.50	24	99
8	Br	*p*-COMe	H	0.50	24	46
9	Br	*p*-COMe	H	1.0	24	99
10	Br	*p*-Cl	H	1.0	24	99
11	Br	*p*-Me	H	1.0	24	71
12	Br	*p*-Me	*o*-Me	0.50	24	54
13	Br	*p*-Me	*o*-Me	1.0	4	65
14	Br	*p*-Me	*o*-Me	1.0	24	92
15	Br	*p*-OMe	*o*-Me	0.50	24	60
16	Br	*p*-OMe	*o*-Me	1.0	4	70
17	Br	*p*-OMe	*o*-Me	1.0	24	86
18	Br	*p*-OMe	*p*-Cl	0.50	24	85
19	Br	*p*-OMe	*p*-Cl	1.0	4	83
20	Br	*p*-OMe	*p*-Cl	1.0	24	99
21	Cl	*p*-OMe	H	1.0	24	–
22	Cl	*p*-COMe	H	1.0	24	73

[a]Reaction conditions: 0.50 mmol of aryl bromide, 0.55 mmol of arylboronic acid, 1.0 mmol of KOH, 4.0 mL of glycerol, 80 °C. [b]Isolated yield. dba: dibenzylideneacetone; Ac: acetate; PCy_3: tricyclohexylphosphine; Ph: phenyl; dppf: 1,1-bis(diphenylphosphino)ferrocene.

Table 4. Catalyst recycling for the Pd-catalyzed Suzuki-Miyaura reaction of bromobenzene with phenylboronic acid in glycerol[a]

Cycle	Ph-Ph yield[b] / %				
	$PdCl_2(PPh_3)_2$ (2.0 mol%)	$PdCl_2$(dppf) (2.0 mol%)	$Pd(OAc)_2$/TPPMS (2.0 mol%)	$Pd(OAc)_2/PPh_2Cl$ (2.0 mol%)	$PdCl_2(PPh_3)_2$ (2.0 mol%)[c] glycerol:MeOH
1	88	86	98	92	89
2	89	28	83	43	92
3	85	19	10	48	86
4	65	–	–	–	99
5	30	–	–	–	99
6	–	–	–	–	77
7	–	–	–	–	62
8	–	–	–	–	31

[a]Reaction conditions: 4.0 mol% of TPPMS or PPh_2Cl, 0.50 mmol of PhBr, 0.55 mmol of $PhB(OH)_2$, 1.0 mmol of KOH, 4.0 mL of glycerol, 80 °C, 24 h. [b]Isolated yield. [c]Glycerol:MeOH (1:1). Ac: acetate; Ph: phenyl; TPPMS: triphenylphosphine monosulfonate sodium salt.

to investigate a glycerol-soluble phosphine, such as the triphenylphosphine monosulfonate sodium salt (TPPMS) that could improve the catalyst homogenization and solubility in the reaction medium. We obtained an excellent yield in the first cycle when 2.0 mol% of $Pd(OAc)_2$/TPPMS was used, but a sharp deactivation of

the catalytic glycerol media was observed again after the first cycle.

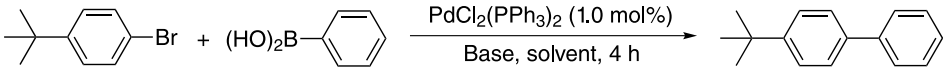
While glycerol does facilitate straightforward product/catalyst separation, it is essential to note that, for the catalysts we evaluated, its recyclability is limited to only a few cycles. During the recycling of the catalyst, we observed precipitation of Pd black, which led to catalyst deactivation and a significant loss of catalytic activity. Despite obtaining colorless organic phases through extraction with hexane, we cannot rule out the possibility of some leaching of Pd and/or the phosphine ligand into the non-polar organic phase during extraction, further contributing to catalyst deactivation. Additionally, there are other issues to consider. The accumulation of inorganic salts in the reaction mixture hindered smooth magnetic stirring, and the viscosity of the glycerol posed challenges. As result, we experimented a 1:1 solution mixture of glycerol and methanol which improved the cycles. However, it is worth noting that a sharp decrease in the yield of the cross-coupling product was observed after five cycles.

Suzuki-Miyaura cross-coupling reaction in triethanolamine:glycerol deep eutectic solvent

To evaluate the performance of triethanolamine:glycerol deep eutectic solvent (TEOA:G DES) in the Suzuki-Miyaura cross-coupling reaction, we initially conducted a comparison with neat glycerol and triethanolamine. Specifically, we reacted 1-bromo-4-*tert*-butylbenzene and phenylboronic acid at 80 ºC for 4 h using 1.0 mol% of $PdCl_2(PPh_3)_2$ as pre-catalyst. The results of these experiments are presented in Table 5. In the presence of KOH as base, the reaction carried out in TEOA:G DES exhibited higher activity compared to glycerol but lower activity than when triethanolamine was used (Table 5, entries 1-3). However, the selectivity showed the opposite trend, with only traces of undesired reduction product, 4-*tert*-butylbenzene, observed in glycerol. The presence of amine groups in the solvent increased the selectivity towards the undesired reduction product to 2% for TEOA:G DES (ca. 2.5 mmol of tertiary amine group *per* mL of solvent) and 7% for triethanolamine (ca. 6.0 mmol of tertiary amine group *per* mL of solvent). In fact, triethylamine have been utilized as source of hydrogen, generating palladium-hydride species responsible for the reduction process.[47] Subsequently, we explored the possibility of conducting the Suzuki-Miyaura cross-coupling reaction without adding any base. In glycerol as the solvent, only traces of the coupling product were obtained (Table 5, entry 4). Encouragingly, when using TEOA:G DES under base-free conditions, the coupling product was achieved with 44% conversion and 98% selectivity after 4 h at 100 ºC, without the need for an additional base (Table 5, entry 8). Also important, regarding both activity and selectivity, TEOA:G DES delivered superior results compared to triethanolamine under these base-free conditions (Table 5, entries 5-8).

After demonstrating the feasibility of the base-free Pd-catalyzed Suzuki-Miyaura reaction in TEOA:G DES, we conducted a screening of various reaction conditions, This investigation included the choice of catalyst precursor, catalyst loading, reaction temperature and reaction time (Table 6). These results were obtained from the GC analysis of the organic phase, which was obtained by extracting the TEOA:G DES medium with hexane. For the coupling of 1-bromo-4-*tert*-butylbenzene with phenylboronic acid, the following trend were observed: (*i*) increasing the

Table 5. Comparison of glycerol, triethanolamine and TEOA:G DES for the Pd-catalyzed Suzuki-Miyaura reaction[a]



entry	Solvent	Base	Temperature / ºC	Conversion[b] / %	Selectivity[b] / %		HC[c] / %
					CC	Red	
1	glycerol	KOH	80	30	> 99	< 1	10
2	ethanolamine	KOH	80	78	93	7	8
3	TEOA:G DES	KOH	80	50	98	2	7
4	glycerol	–	80	< 0.5	100	–	–
5	ethanolamine	–	80	6.5	94	6	3
6	TEOA:G DES	–	80	24	98	2	4
7	ethanolamine	–	100	39	92	8	14
8	TEOA:G DES	–	100	44	98	2	13

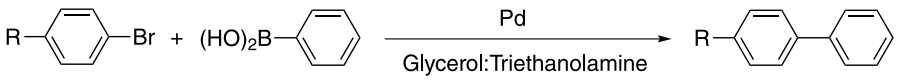
[a]Reaction conditions: 1.0 mol% $PdCl_2(PPh_3)_2$, 1.0 mmol of 4-*t*BuPhBr, 1.1 mmol of $PhB(OH)_2$, 1.1 mmol of KOH, 4.0 mL of solvent, 4 h. [b]Conversion of 4-*t*BuPhBr and selectivity for cross-coupling product 4-*t*BuPhPh (CC) and reduction product 4-*t*BuPh (Red) were determined by GC. [c]Yields of homocoupling product PhPh (HC) were determined by GC based on starting $PhB(OH)_2$. TEOA:G DES: triethanolamine:glycerol deep eutectic solvent.

temperature led to higher activity; however, it also resulted in increased formation of by products, including reduction and homocoupling products (Table 6, entries 1, 2 and 4). (*ii*) The reaction could be conducted with ligand-free catalyst precursors, such as $Pd(OAc)_2$ and $Pd(dba)_2$, but they exhibited lower activity and selectivity compare to $PdCl_2(PPh_3)_2$ (Table 6, entries 5, 7 and 9, and entries 4, 8 and 10). (*iii*) Elevating the catalyst loading of $PdCl_2(PPh_3)_2$ increased activity, but also the formation of reduction and homocoupling by-products (Table 6, entries 2-5, 11 and 12). (*iv*) It is worth noting that an efficient stirring system is crucial for achieving high conversion and reproducible results. Based on these findings, we achieved complete conversion of 4-bromoanisole and 98% selectivity of coupling product by conducting the reaction at 100 ºC for 22 h, utilizing 2.0 mol% of $PdCl_2(PPh_3)_2$ (Table 6, entry 12).

Next, we applied the optimized conditions, which were carried out in the absence of inorganic bases, for the cross-coupling of various of aryl bromides with different arylboronic acids to investigate the versatility of this protocol (Table 7). We are delighted to see that aryl bromides and aryl boronic acids containing both electron releasing and withdrawing functional groups could be effectively coupled without the need for additional base, resulting in moderate to good yields of biphenyl products. The cross-coupling products were readily isolated by hexane extraction, yielding purities ranging from 92 to 98%, as determined by GC. The primary by-product observed was the homocoupling of the arylboronic acid. In cases where the purity of coupling product below 96%, an additional chromatography separation step was necessary.

In the course of optimization studies, we identified the generation of a by-product through GC-MS analysis in reactions characterized by low conversion rates (Figure S7, SI section). The MS equipment's software indicated similarity between the MS-spectra's main fragmentations of this peak and those of triethanolamine borate, which is triethanolamine ester of boric acid. In order to confirm the origin of this peak, we synthesize triethanolamine borate from the condensation reaction of boric acid with triethanolamine in water,[48] and the borate obtained exhibited the same retention time (16.9 min) and mass spectra as those observed via GC-MS for the cross-coupling reaction. These observations led us to investigate the formation of triethanolamine boronates resulting from the condensation of phenylboronic acid with triethanolamine (**1**, Scheme 3) and 4-methoxyphenylboronic with triethanolamine (**2**, Scheme 4). For this, we conducted a procedure similar to that used to obtain glycerol arylboronantes (Scheme 1), which involving reacting phenylboronic acid and triethanolamine in THF. Furthermore, we fully characterized compounds **1** and **2** through IR, HRMS, ^{1}H, ^{13}C and ^{11}B NMR. The

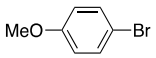
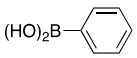
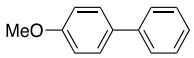
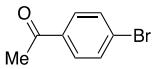
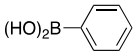
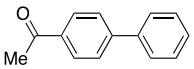
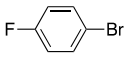
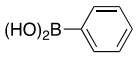
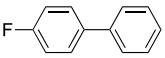
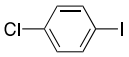
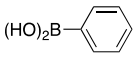
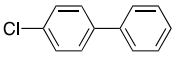
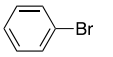
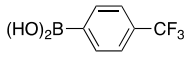
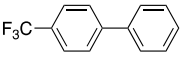
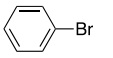
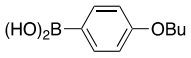
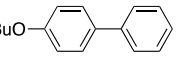
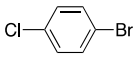
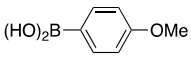
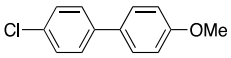
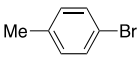
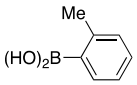
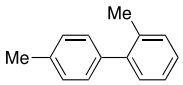
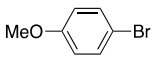
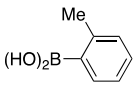
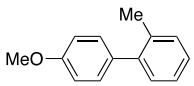
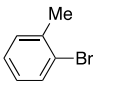
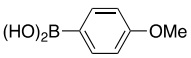
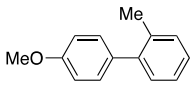
Table 6. Screening of reaction conditions for the base-free Pd-catalyzed Suzuki-Miyaura reaction in triethanolamine:glycerol DES[a]



entry	Catalyst / mol%	R	Temperature / ºC	time / h	Conversion[b] / %[b]	Selectivity[b] / %		HC[c] / %
						CC	Red	
1	$PdCl_2(PPh_3)_2$ (1)	*t*Bu	80	4	24	98	2	4
2	$PdCl_2(PPh_3)_2$ (1)	*t*Bu	100	4	44	98	2	13
3	$PdCl_2(PPh_3)_2$ (2)	*t*Bu	100	4	64	98	2	22
4	$PdCl_2(PPh_3)_2$ (1)	*t*Bu	120	4	93	85	15	11
5	$PdCl_2(PPh_3)_2$ (0.5)	*t*Bu	120	4	74	95	5	6
6	$PdCl_2(PPh_3)_2$ (0.5)	*t*Bu	120	24	91	98	2	4
7	$Pd(OAc)_2$ (0.5)	*t*Bu	120	4	44	95	5	1
8	$Pd(OAc)_2$ (1)	*t*Bu	120	4	59	93	7	2
9	$Pd(dba)_2$ (0.5)	*t*Bu	120	4	39	89	11	1
10	$Pd(dba)_2$ (1)	*t*Bu	120	4	46	87	11	2
11	$PdCl_2(PPh_3)_2$ (1)	OMe	100	24	32	100	–	–
12	$PdCl_2(PPh_3)_2$ (2)	OMe	100	22	100	98	2	2
13	$PdCl_2(PPh_3)_2$ (2)	OMe	80	22	90	99	1	–

[a]Reaction conditions: 1.0 mmol of ArBr, 1.1 mmol of $PhB(OH)_2$, 4.0 mL of TEOA:G DES. [b]Conversion of 4-*t*BuPhBr and selectivity for cross-coupling product 4-*t*BuPhPh (CC) and reduction product 4-*t*BuPh (Red) were determined by GC. [c]Yields of homocoupling product PhPh (HC) were determined by GC based on starting $PhB(OH)_2$.

Table 7. Substrate scope of the cross-coupling reaction under inorganic base-free conditions in triethanolamine:glycerol DES[a]

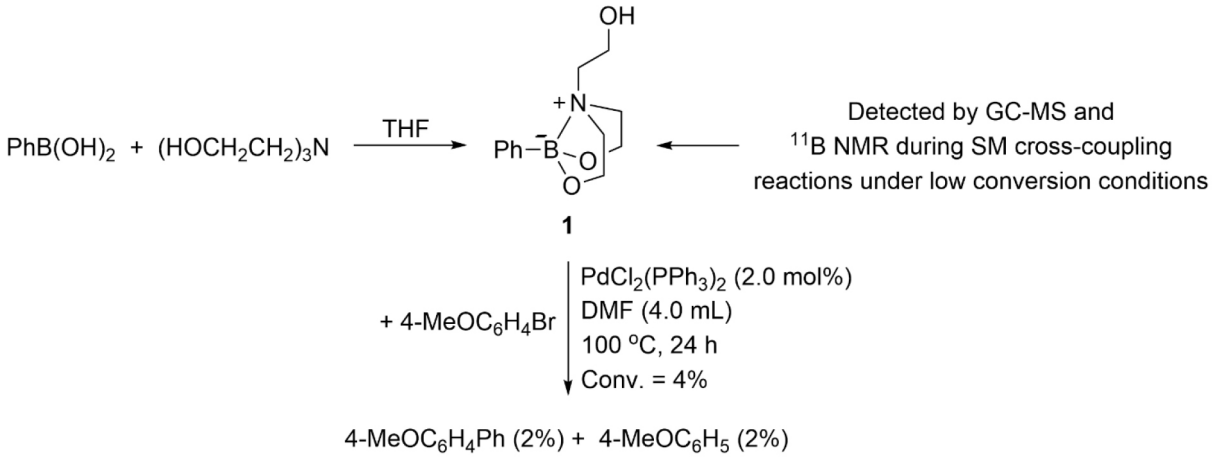
entry	ArX	Ar'B(OH)$_2$	Ar-Ar'	Yield[b] / %
1				54
2[c]				78
3				70
4[c]				45
5				72
6				58
7				42
8				40
9				62
10				50

[a]Reaction conditions: 2.0 mol% of $PdCl_2(PPh_3)_2$, 1.0 mmol of ArBr, 1.1 mmol of Ar'$(OH)_2$, 4.0 mL of TEOA:G DES, 20-24 h. [b]Isolated yields. [c]1.0 mol% of $PdCl_2(PPh_3)_2$.

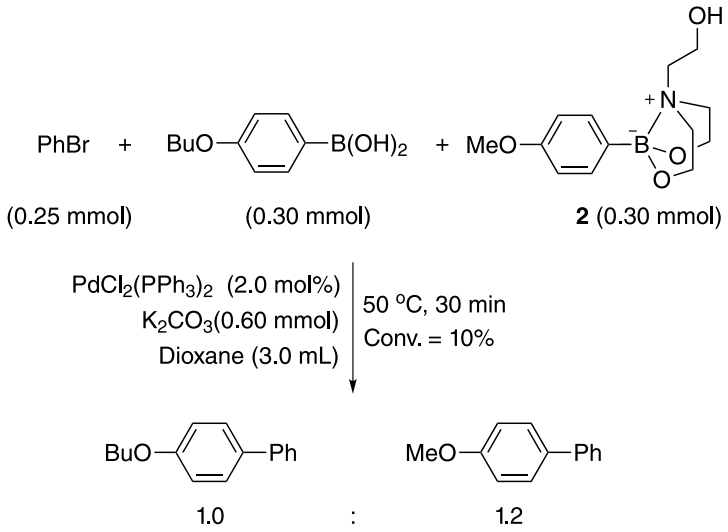
transformation of the sp^2-hybridized boronic acids into the tetrahedral, sp^3-hybridized, boronate esters was confirmed by ^{11}B NMR spectroscopy.[49] Typically, arylboronic acids have ^{11}B chemical shift around 30 ppm,[50] while glycerol phenylboronate exhibits a shift of 31.6 ppm (see SI section). Upon coordination of the nitrogen to the boron atom decreases, the chemical shift of triethanolamine boronates **1** and **2** decrease to 12.9 and 13.1 ppm, respectively. Notably, ^{11}B chemical shifts around 12 ppm in aprotic solvents have also been reported for diethanolamine boronates,[51] and the coordination of the nitrogen for the diethanolamine boronates was also further validate in the solid state via X-ray crystallographic analysis.[52]

It is worthwhile to mention that the compounds **1** and **2** exhibited the same retention time and mass spectra as those observed via GC-MS for the cross-coupling reaction and for the isolated triethanolamine borate. These observations strongly suggest that the boronates **1** and **2** must decomposed to triethanolamine borate in the GC-MS injector. Therefore, we needed another experiment to unequivocally demonstrate that triethanolamine boronate is formed *in situ* during the cross-coupling reaction. Therefore, we ran the reaction of 4-bromoanisole with phenylboronic acid in TEOA:G DES for two hours. Then, CD_3OD was added, and the mixture was analyzed by ^{11}B NMR (see SI section). No peak around 30 ppm was observed indicating total consumption of phenylboronic acid. Moreover, peaks around 10 pm were observed showing the presence of **1** and triethanolamine borate.

Diethanolamine boronates have previously been employed as coupling partner for the base-free cross-coupling reaction with diazonium salts.[53] However, for Suzuki-Miyaura coupling involving diethanolamine boronates, the use of an inorganic base is necessary.[54] With triethanolamine phenylboronate in hands, we investigated its reactivity in cross-coupling reactions. We observed that the cross-coupling yield for the reaction with triethanolamine phenylboronates was only 2% in dimethylformamide under base-free conditions (Scheme 3). Then, we conducted a competitive experiment to assess the relative reactivity triethanolamine boronate compared to boronic acid (Scheme 4). A mixture of triethanolamine 4-methoxyphenylboronate (**2**) and 4-butoxyphenylboronic acid was subjected to a cross-coupling reaction with



Scheme 3. Synthesis of triethanolamine phenylboronate **1** and its reactivity for the cross-coupling reaction under base-free conditions.



Scheme 4. Comparative reactivity of triethanolamine arylboronate and arylboronic acid in the Suzuki-Miayura cross-coupling reaction.

bromobenzene. The activity was evaluated at low conversion to compare the initial rates. Similar to our earlier findings with glycerol boronates,[24] triethanolamine boronate exhibited activity comparable activity to boronic acid, with a slight preference for the coupling reaction with boronate ester (1.2:1.0 relative ratio).

Conclusions

In conclusion, both glycerol and glycerol-triethanolamine deep eutectic solvent (TEOA:G DES) offer environmentally friendly, cost-effective, and practical protocols for Pd-catalyzed Suzuki-Miyaura cross-coupling of aryl halides with arylboronic acids. In both solvents, the cross-coupling products can be easily extracted with hexane. In the case of glycerol, the addition of an inorganic base such as KOH is necessary, and excellent yields (up to 99%) were obtained using $PdCl_2(PPh_3)_2$ as catalyst precursor. However, the recyclability of the glycerol medium containing the catalyst is limited to a few cycles. Additionally, we explored the use of chlorodiphenylphosphine as a pre-ligand and, even though glycerol phosphinite does not form *in situ*, PPh_2Cl proved to be an excellent pre-ligand.

Glycerol-triethanolamine deep eutectic solvent, on the other hand, outperforms glycerol when used in conjunction with KOH as a base. More importantly, it allows the cross-coupling reaction to proceed under inorganic base-free conditions. Consequently, we successfully demonstrated that aryl bromides and aryl boronic acids, regardless of their electron releasing or attracting functional groups, can be coupled without the need for additional base, resulting in moderate to good yields of biphenyl products. Moreover, we observed the formation of triethanolamine phenylboronate during the reaction. The triethanolamine boronate was subsequently synthesized through the condensation of phenylboronic acid with triethanolamine and its coordination to the boron atom was confirmed by ^{11}B NMR spectroscopy.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

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