Sustainable Pd-Catalyzed Direct Arylation of Thienyl Derivatives with (Hetero)aromatic Bromides under Air in Deep Eutectic Solvents

Francesco D'Amico, Costanza Papucci, Daniele Franchi, Gianna Reginato, Massimo Calamante, Lorenzo Zani,* Alessio Dessì,* and Alessandro Mordini

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ABSTRACT: An optimized protocol for the Pd-catalyzed direct arylation of 3,4-ethylenedioxythiophene (EDOT) and other substituted thiophenes with (hetero)aromatic bromides in a deep eutectic solvent made of a mixture of choline chloride/glycerol (1:2) is presented. The coupling reactions have been successfully run under air, in nonanhydrous conditions, using $PdCl_2$ as a palladium source, with a catalyst loading as low as 1 mol %. The adjustment of each reaction component allowed finding robust conditions for the introduction of both electron-poor and electron-rich (hetero)aryl bromides with moderate-to-high yields. The sustainability of the protocol was established through calculations of green metrics, such as Eco-scale and E-factor, and compared with the literature, when possible. Remarkably, such procedure can

DIRECT ARYLATION IN DESs — Under air no water exclusion — 110 °C, 24 h — + $PdCl_2$, P(2-MeOPh), K_2CO_3, Pivalic acid — 15 examples, Economic reagents, Catalyst loading as low as 1 mol%, Yields: up to 94%, Eco-scale: up to 81

be successfully applied for the simple preparation of conjugated organic compounds with potential applications in optoelectronics, as we have shown, by obtaining two molecules previously reported as a hole transport material for perovskite solar cells and the final intermediate of a photosensitizer for dye-sensitized solar cells.

KEYWORDS: C−H activation, cross-coupling reactions, deep eutectic solvents, palladium catalysis, sustainability, green metrics, thienyl derivatives
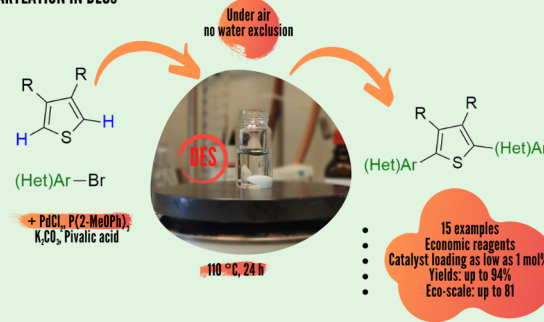
INTRODUCTION

Among the 12 Green Chemistry Principles, introduced by Paul Anastas and John Warner in 1998,[1] the presence of a specific statement encouraging the use of safer solvents and auxiliaries highlights how crucial solvent selection is in the design of a new chemical process. Solvents' choice is often underestimated in academic research, but they account for about 80−90% of the total mass in a classic batch operation for the synthesis of fine chemicals and/or pharmaceutical products, representing most of the waste at the end of the process.[2] The problem becomes particularly tricky when volatile organic solvents (VOCs), which are the most common choice both at the laboratory and industrial scale, are employed since they are usually endowed with toxicity and flammability issues, which make the chemical process not sustainable from an environmental point of view. To help chemists in selecting the "greenest" solvent for the design of more sustainable processes, the Innovative Medicine Initiative CHEM21 provided detailed guidelines based on safety, health, and environmental (SH&E) criteria for the ranking of 75 different solvents.[3] At the same time, the use of other emerging greener solvent classes, such as ionic liquids, fluorinated solvents, and switchable solvents,[4] is increasingly widespread.

An alternative solution, which has been introduced at the beginning of the century[5] and has quickly captured the attention of academic and industrial researchers, is represented by deep eutectic solvents (DESs). A DES is a liquid eutectic mixture of two or more solid components having a lower freezing point than those of the single constituents due to the formation of a thick network of hydrogen bonds.[6,7] Typically, the two components are Lewis or Brønsted acids and bases, which are, respectively, defined as a hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD), bearing different types of cations and anions. The synthesis of a DES is straightforward since it involves just mixing the proper amounts of the selected HBD and HBA and then heating and stirring the mixture until a colorless liquid is formed. The simple zero-waste synthesis, the possibility of using inexpensive and environmentally benign components, and their unique physicochemical properties[8] like low volatility and high

thermal stability make DESs extremely appropriate for many applications,[9] such as extraction of bioactive compounds,[10,11] processing of biomass,[12−14] and CO_2 capture,[15] ranging from analytical chemistry[16,17] to electrochemistry[18] and materials chemistry.[19,20]

Furthermore, taking advantage of some peculiar properties like high viscosity, conductivity, and polarity, as well as high solubility in water, which usually simplify the isolation of the final products, DESs have been successfully employed as alternatives to VOCs in many organic and organometallic transformations.[21−28] For example, the employment of polar organometallic reagents like alkyl- and aryllithium species[29,30] in DESs has been successfully proven under mild conditions and very short reaction times. A very important class of transformations that were positively affected by the use of DESs consist of cross-coupling reactions,[31] as reported for Suzuki−Miyaura,[32−36] Sonogashira,[33,34,37] Hiyama,[33,38] Negishi,[39] Stille−Migita,[40] and Ullmann-type[41−44] reactions, which have been extensively investigated in recent years.

In the field of cross-coupling reactions, direct arylation (DA) processes have recently gained a special prominence,[45] as they allow the formation of a new carbon−carbon bond starting from a (hetero)aromatic halide and a (hetero)arene, bearing one or more $C(sp^2)$−H bonds (Scheme 1), without a need of preformed organometallic reagents, improving several aspects such as time, waste generation, and atom economy. In particular, since heteroarenes containing reactive C−H bonds like thiophenes, pyrroles, imidazoles, and thiazoles are fundamental building blocks for the preparation of small valuable molecules in the field of organic electronics and photovoltaics,[46,47] DA reactions are found extremely efficient for such applications. Indeed, we have already successfully applied DA procedures to the preparation of several organic photoactive compounds, such as molecular sensitizers for dye-sensitized solar cells (DSSCs)[48,49] and thienopyrazine-based fluorophores with NIR emission.[50] Unfortunately, DA reactions are usually run in aromatic solvents (Scheme 1) like toluene or aprotic polar media like N,N-dimethylformamide (DMF) or N,N-dimethylacetamide (DMAc), which are, respectively, defined as "problematic" and "hazardous" by the CHEM21 solvent guide[3] because of health, environmental, and safety issues. For this reason, greener alternatives have been investigated and, in the last decade, DA reactions have been carried out in more environmentally friendly reaction media like cyclopentyl methyl ether,[51] dialkyl carbonates,[52,53] alcohols,[53] γ-valerolactone,[54] Rhodiasolv Polarclean,[55] ionic liquids,[56] and even water.[52,57]

DESs have been employed as green solvents for DA reactions too, but, to the best of our knowledge, only two examples were reported in the literature so far. The first article was published in 2017 by Farinola et al. and described the double direct arylation of 5-octylthieno[3,4-c]pyrrole-4,6-dione with aryl iodides in a choline chloride (ChCl)/urea (1:2) mixture (Scheme 2a):[58] the reaction goes smoothly to the coupling products if iodobenzene or alkyl-substituted aryl iodides are employed. When aryl iodides bearing more polar functional groups like ketones, esters, ethers, and nitro groups

Scheme 1. Generic Scheme of a Direct Arylation Reaction
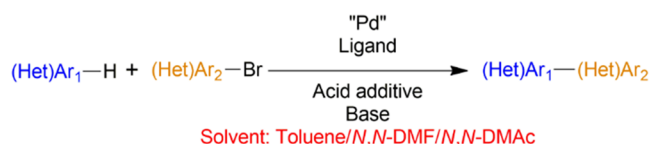
Scheme 2. DA Reaction of (a) 5-Octylthieno[3,4-c]pyrrole-4,6-dione with Aryl Iodides in DESs Together with an Organic Cosolvent; (b) Imidazoles with Aryl Bromides and a Magnetic Pd-Based Catalyst in DESs; and (c) 3,4-Disubstituted Thiophenes with Aromatic Bromides in DESs
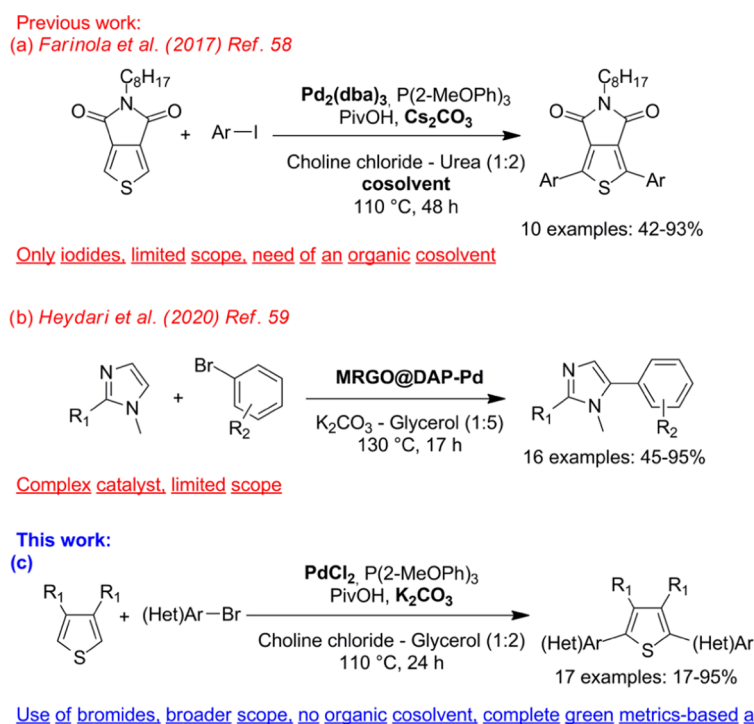
Scheme 3. Model DA Reaction of EDOT (1) with Halobenzenes. Conditions: 1 (1.0 equiv −0.3 mM); 2a or 3 (2.5 equiv); [Pd] (5.0 mol %); Ligand (10 mol % If Monodentate, Otherwise 5 mol %); Additive (30 mol %); Base (2.5 equiv), ChCl/Gly 1:2, 110 °C, 24 h
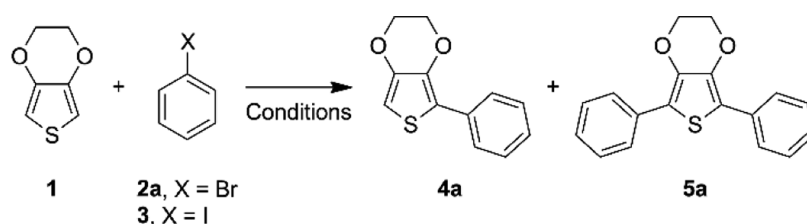
were used, the addition of small amounts of an organic solvent like cyclopentyl methyl ether was necessary to obtain good yields. Although this seminal protocol paved the way for the study of DA reactions in DESs, it still suffered from some drawbacks like the need for a cosolvent, the exclusive use of iodides as reaction partners, and the use of a quite expensive precatalyst and base. The second example was reported in 2020 by Heydari and co-workers,[59] who investigated the arylation in the 5-position of 1-methyl-2-alkyl-1H-imidazoles using several aryl bromides in a mixture of K_2CO_3/glycerol (Gly) 1:5 (Scheme 2b) and obtaining the coupling products in fair to high yields (45−95%). The catalyst employed was a 2,6-diaminopyridine−amidoxime palladium complex immobilized on the magnetic reduced graphene oxide (**MRGO@DAP-Pd**), which proved to be highly efficient, but the complexity and the length of its five-step synthesis hamper a further extension of the scope of such procedure. Furthermore, in both cases, no sustainability assessment of those protocols by calculation of the relevant green metrics was presented by the authors.

Considering these precedents and based on our research experience in the synthesis of organic photoactive compounds,[48−50,60,61] we were prompted to further investigate the DA reaction of thiophene derivatives in DESs, aiming at finding efficient conditions for the preparation of structures of potential interest in the field of organic electronics and photovoltaics. Herein, we report on the arylation of a series of 3,4-disubstituted thiophenes with (hetero)aromatic bromides in a ChCl/Gly (1:2) mixture under air, employing easily available and low-cost reagents like palladium chloride and potassium carbonate (Scheme 2c). Under these conditions, the possibility to employ bromides containing different functional groups like ketones, aldehydes, nitriles, and carboxylic acids was demonstrated. Additionally, the procedure proved feasible for the preparation of small molecules already described in the literature for photovoltaic applications like a hole transport material (HTM)[62] for perovskite solar cells (PSCs) and an advanced intermediate for the synthesis of a photosensitizer for dye-sensitized solar cells (DSSCs).[63] Finally, for the first time, E-factor[64,65] and Eco-scale[66] values have been calculated for every reaction and, when possible, compared with the literature, to introduce a "quantitative" assessment of the procedure in terms of sustainability.

RESULTS AND DISCUSSION

3,4-Ethylenedioxythiophene (EDOT 1) is a ubiquitous building block found in many small molecules and polymers with application in optoelectronics, ranging from photovoltaics (photosensitizers[63] for DSSCs and HTMs[62] for PSCs) to semiconductors[67,68] and electrochromes.[69,70] For this reason, we chose the double arylation of EDOT (Scheme 3) as a model reaction and investigated the effect of changing all of the

reaction components, that is, the halide, palladium precatalyst, ligand, acid additive, and base. To design a straightforward and potentially scalable protocol, all reactions were run under air without any control of humidity. Initially, for the optimization of the reaction conditions, we selected a ChCl/Gly (1:2) mixture as a DES since it is endowed with high biocompatibility and biodegradability[10] and has optimal tolerance toward classic cross-coupling reactions.[32,33] The complete list of the initial optimization tests is reported in the Supporting Information (Table S1).

First, the effect of the nature of the halide (bromobenzene 2a vs iodobenzene 3) on the arylation of EDOT 1 was evaluated under ligandless conditions (Table S1, entries 1−2), using Pd(OAc)$_2$ as a catalyst, pivalic acid (PivOH) as an additive, and K_2CO_3 as a base: the solid mixture was dissolved in ChCl/Gly (1:2) and stirred at 110 °C for 24 h. At the end of the reactions, the composition of the crudes was analyzed via ^{1}H-NMR spectroscopy: in both cases, only a partial conversion of 1−5a was achieved, and the product of a single arylation (4a) was found as the main component. Nevertheless, the slightly higher conversion obtained when 2a was used prompted us to employ the more affordable bromide instead of iodide for the following optimization work.

Several phosphine ligands were tested (Table S1, entries 3−19), resulting in significantly increased EDOT conversions when compared to the test in the absence of ligands. Initially, we examined (hetero)aromatic phosphines (Table S17, entries 3−7) bearing different steric hindrance and electron-donating properties, and the best result was obtained with P(2-MeOPh)$_3$, in the presence of which only traces of both 1 and 4a were found in the crude and a 90% yield of 5a was achieved. Since the success of the reaction seemed to be linked to the right balance of electronic and steric properties of the ligand, alkyl phosphines were tested as well (Table S1, entries 8−10). The best result was obtained with P(t-Bu)$_3$·HBF$_4$ but the observed 69% yield of 5a was still lower than that obtained with P(2-MeOPh)$_3$. No yield improvement was obtained employing Buchwald-type dialkylbiaryl phosphine ligands[71] (Table S1, entries 11−14), while, among bidentate ligands (Table S1, entries 15−19), XantPhos provided an almost complete conversion of 1 and an 85% yield of 5a. This excellent result was in good agreement with the reaction mechanism reported by Blackmond et al.,[72] according to which the active catalyst in the presence of a base, air, and humidity is a hemilabile Pd-XantPhos mono-oxide complex, able to move from the bidentate coordination to monodentate depending on the need in the catalytic cycle. Considering all of the attempts, the best ligand in terms of conversion of starting materials and the isolated yield of product 5a was P(2-MeOPh)$_3$, which was therefore selected for further optimization work.

Scheme 4. Pd-Catalyzed DA Reaction of EDOT (1) with (Hetero)aryl Bromides (2a–k) in DESs under Air (top) and the Corresponding Products (5a–k) (bottom)
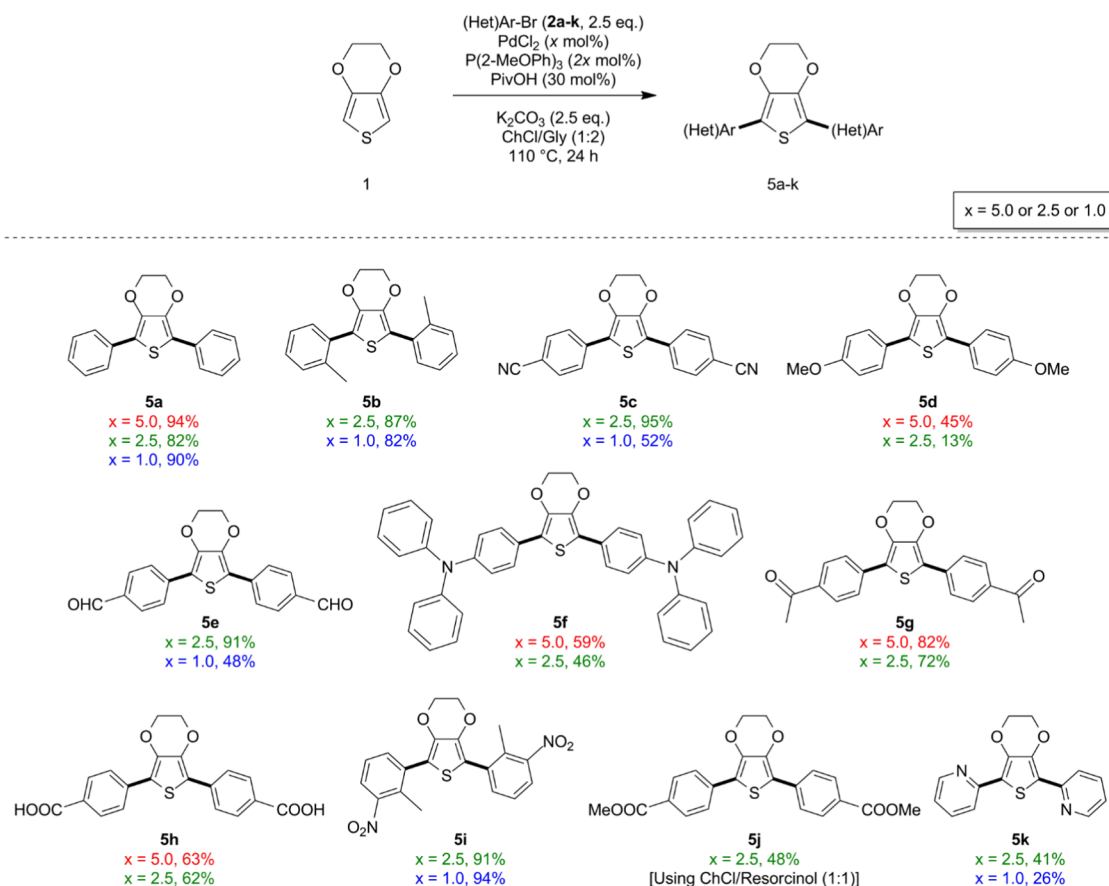
The presence of palladium was proven essential for the reaction to occur (Table S1, entry 20), while no significant difference in terms of conversion of starting materials was observed employing other Pd(0) or Pd(II) precatalysts than Pd(OAc)$_2$ (Table S1, entries 21−23). In particular, PdCl$_2$, which is the most economic and widely available palladium source, was able to afford the product with a very high yield (94%). PdCl$_2$ is scarcely used for cross-coupling reactions because of its very low solubility in the most common organic solvents, but, on the contrary, this precatalyst can be completely dissolved in a ChCl-based DES at the reaction temperature, thanks to the presence of chloride anions, which form soluble PdCl$_4^{2-}$ complexes in situ.[73] For these reasons, PdCl$_2$ was chosen as the precatalyst for the following reactions. The absence of an acid additive, as well as the employment of acetic acid, did not hamper the reaction (Table S1, entries 24−25) but decreased the conversion of 1 to 5a, proving that the presence of pivalic acid was fundamental to speed up the reaction. Finally, we tested the reaction both in the absence and in the presence of different bases than K$_2$CO$_3$ (Table S1, entries 26−28). As expected, the reaction did not even start without a base, while similar starting material conversions were obtained with all carbonates, prompting us to select the common and inexpensive K$_2$CO$_3$.

Once the best combination of reagents was selected, we investigated the effect of the catalyst loading and the reaction time on the reaction outcome (Table S2). Using 5.0 mol % PdCl$_2$, the reaction time could be decreased to six hours without affecting the product yield, while a further reduction to

four hours left some unreacted starting materials (Table S2, entries 1−3). On the contrary, 24 h was necessary to obtain high conversion of the starting material conversion when the Pd loading was reduced to 2.5 mol % and even to 1.0 mol % (Table S2, entries 4−7). Even using such catalyst loadings, a 90% yield of 5a was obtained after purification by crystallization from ethanol (Table S2, entry 8).

We finally concluded the optimization study by investigating the use of alternative DES mixtures (Table S3). Different HBDs were tested while keeping ChCl as a HBA: while ethylene glycol and resorcinol were found to be possible alternatives to glycerol, albeit providing lower yields of 5a (Table S2, entries 2−3), urea and fructose gave unsatisfactory conversion values of EDOT 1 (Table S2, entries 4−5). The use of a eutectic mixture of ethylene glycol and K$_2$CO$_3$ (10:1)[74] could be intriguing since, in that case, the HBA could also act simultaneously as a base but only a partial conversion of 1 to 5a was achieved (Table S3, entry 6). Another unsatisfactory result was obtained employing methyltriphenylphosphonium bromide (MTPPBr) as the HBA in combination with glycerol, the best performing HBD in combination with ChCl (Table S3, entry 7). Finally, even lipophilic DESs have been taken into account for the DA reaction (Table S2, entries 8−9). While a combination of decanoic acid and tetrabutylammonium bromide (TBAB) (1:2) was completely ineffective in the direct arylation of EDOT, a mixture of TBAB and n-undecanol (1:1) provided promising results, with a high conversion of the starting material (≈86%, Table S2, entry 9) to 4a and 5a. Since a

Table 1. Green Metrics of the Best DA Reaction of EDOT 5 with (Hetero)aryl Bromides 2a-k and the Corresponding Literature Comparison

product	"Pd" loading (mol %)	E-factor (excluding purification)	purification method[a]	E-factor (including purification)	eco-scale[b]	eco-scale (lit.)[c]
5a	1.0	21	R.	52	71	47[75]
5b	2.5	22	F.C.	351	63	
5c	2.5	23	R.	83	79	0[76]
5d	5.0	50	F.C.	2331	46	48[77]
5e	2.5	24	R.	87	81	2[78]
5f	5.0	21	R.	78	62	53[75]
5g	5.0	24	R.	88	77	32[79]
5h	5.0	31	R.	142	67	
5i	1.0	15	R.	41	80	
5j	2.5	39	R.	138	50	
5k	2.5	60	F.C.	4279	41	−71[80]

[a]R.: recrystallization; F.C.: flash chromatography. [b]Calculated using the experimental data reported in the SI. [c]Calculated using the experimental data reported in the corresponding articles.

Scheme 5. Pd-Catalyzed DA Reaction of 3,4-Disubstituted Thiophenes (6, 9a,b) with Aryl Bromides (2a,c,e) in DESs under Air and the Corresponding Products (8, 10a−c)
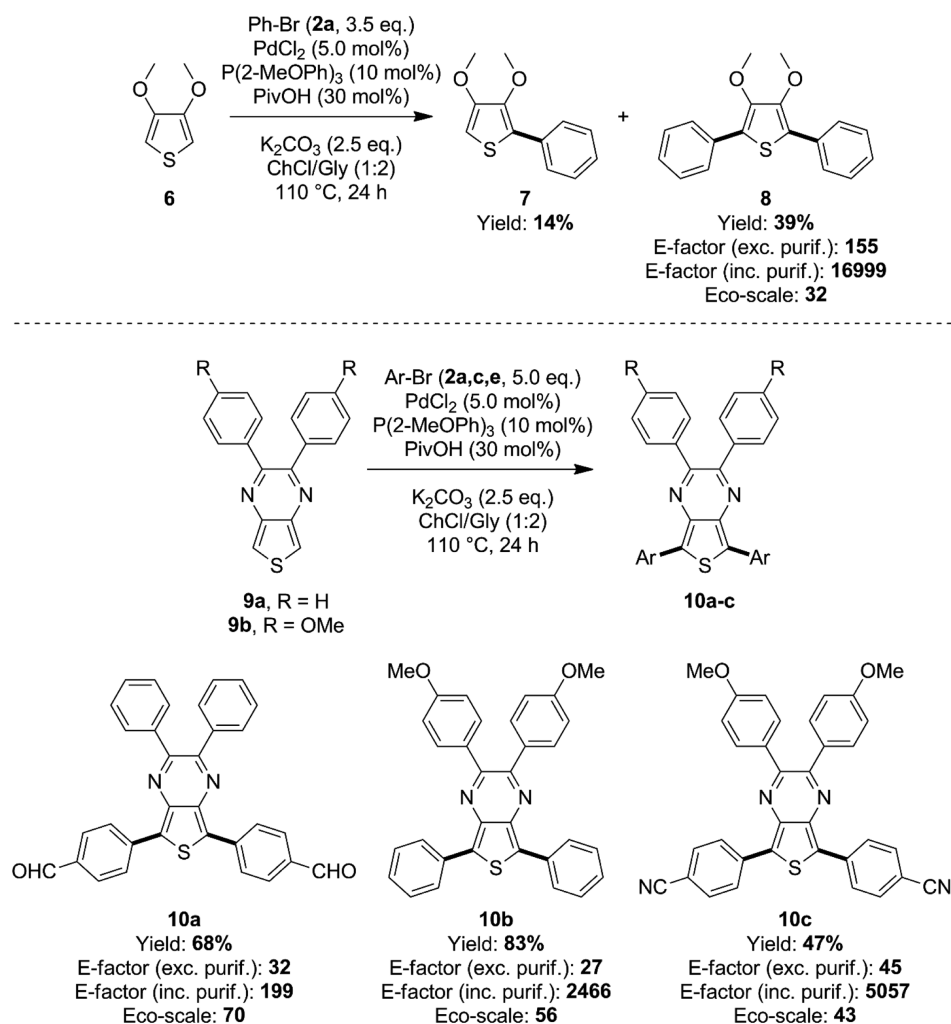
lipophilic DES could not be removed with liquid−liquid extraction and precipitation of the product was more demanding, the ChCl/Gly (1:2) mixture was chosen as the best performing for DA reactions.

With the best conditions in our hands, we explored the scope of the reaction in DESs employing several (hetero)-aromatic bromides (2a−k) containing different functional groups (Scheme 4). The catalyst loading was varied from 5.0 to 1.0 mol %. Reaction yields are reported in Table 1, as well as the E-factor and the Eco-scale values, together with a literature comparison, when possible. All of the details of the calculations are listed in the SI.

The protocol tolerates almost every functional group we tested, including nitriles (5c), ethers (5d), aldehydes (5e),

ketones (**5g**), carboxylic acids (**5h**), and nitro groups (**5i**), with the exception of esters, as in bromide **2j**. The latter was probably unstable in the reaction conditions since it underwent quick transesterification with the glycerol present in the DES. Gratifyingly, we found that substituting glycerol with resorcinol as the HBD of the DES allowed the isolation of the desired product **5j** with a fair yield. Generally, electron-poor bromides (**2c,e,g−j**) were found to be more reactive, providing complete conversions of the starting material and very high yields even with low catalyst loadings, down to 1.0 mol %, while the reaction with electron-rich bromides (**2d,f**) was more sluggish and a Pd loading as high as 5.0 mol % was necessary to obtain good yields. Moreover, *ortho*-substitution (**2b,i**) was not detrimental for the reaction course, and even heteroaromatic bromides like 2-bromopyridine **2k** were reactive under our experimental conditions, albeit with only moderate yields. Finally, it should be highlighted that in many cases, purification of the products by flash column chromatography was not necessary, and isolation of the final products could be carried out by means of simple recrystallization from environmentally friendly solvents such as EtOH (**5a,c,e,g−j**) or EtOAc (**5f**).

To evaluate the *greenness* of our DES-based DA protocol, *E*-factor and Eco-scale values of our reactions were calculated and, when possible, compared with the same transformations already described in the literature (Table 1). Details of the calculations are reported in the SI. Initially, we only took into account the contribution of the reaction process to the *E*-factor, excluding workup and purification materials from the calculations. Low *E*-factors ranging from 15 to 60 were obtained, in agreement with other literature works concerning related cross-coupling reactions in DESs following the same convention.[32,37,81] However, we believe that the synthetic process has to be evaluated as a whole to assess its overall sustainability; therefore, all of the calculations were repeated including the waste stemming from the reaction, the workup procedure, and also the purification. Obviously, all of the *E*-factors increased (Table 1), but fell in the 41−142 range when product purification was carried out by recrystallization, with values exceeding 100 observed only in those cases where complete conversion of the starting materials could not be achieved (**5h,j**). As we could expect, recurring to flash chromatography caused a significant increase of *E*-factors, with values ranging between 351 and 4279 (**5b,d,k**). However, all our values look similar to others calculated according to the same principles.[77,82]

Eco-scale values ranged from 41 to 81: according to the original paper by Van Aken et al.,[66] the reaction conditions in DESs can thus be ranked as "*excellent*" (Eco-scale >75) for the preparation of compounds **5c,e,g,i**, and "*acceptable*" (Eco-scale >50) for compounds **5a,b,f,h,j**. Therefore, "*inadequate*" (Eco-scale <50) values were obtained only for the preparation of **5d,k**, mostly due to the lower isolated yields of those compounds. Importantly, a comparison with the synthesis of the same compounds described in the literature showed that in almost all cases, the Eco-scale values were significantly increased thanks to the application of the DA protocol in DESs. The only exception was that of product **5d**, for which Eco-scale values from our procedure and the literature[77] were almost the same since both were based on a DA reaction in a neoteric and sustainable solvent (DES vs micelles in water), and **5d** was one of the few products that could not be isolated by crystallization, requiring flash chromatography in the purification step.

After testing the arylation of EDOT (**1**) with different bromides, the scope of the DA protocol in DESs was extended to differently substituted thiophenes (**6**, **9a,b**; Scheme 5). Under the previously optimized conditions, 3,4-dimethoxythiophene (**6**) showed an incomplete conversion of around 60% in the same time (24 h), despite featuring similar electronic properties as EDOT. We can hypothesize that the higher rotational degree of freedom of the methoxy group in the 3-position of **6** could hamper the formation of the transition state in the concerted metalation−deprotonation (CMD) pathway (Figure 1),[46,77,83] thus slowing down the reaction kinetics.
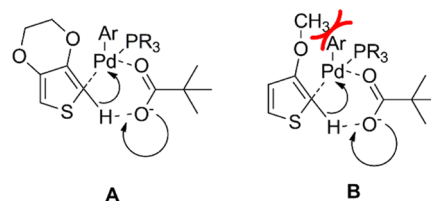

Figure 1. Carboxylate-assisted concerted metalation−deprotonation (CMD) transition state for EDOT (A) and 3,4-dimethoxythiophene (B).

Accordingly, product **8** was isolated in 39% yield, which was nevertheless similar to what was obtained for previously reported DA reactions of 3-methoxythiophene in conventional solvents.[84] Unfortunately, a laborious chromatographic purification proved necessary to separate the desired product from intermediate **7** (isolated in 14% yield), which worsened the green metric values (*E*-factor: 16999; Eco-scale: 32).

More interesting was the behavior of thieno[3,4-*b*]pyrazines **9a,b** (Scheme 5), which were smoothly converted into the corresponding bis-arylated products **10a−c** with fair to good yields (47−83%). Including in the *E*-factor calculation only the contribution to the waste stemming from the reaction, low values in the 27−45 range were obtained in all cases. Again, a more realistic scenario was depicted taking into account all solvents and materials required for workup and purification: the possibility of purifying *bis*-aldehyde **10a** by crystallization allowed us to achieve a low *E*-factor (199) and a good Eco-scale (70) parameter. On the other hand, compounds **10b,c** required purification by flash chromatography, resulting in one order of magnitude higher *E*-factors while maintaining fair Eco-scale values (43−56). Interestingly, these syntheses demonstrated the feasibility of our DA protocol for the quick assembly of organic materials with promising light-emitting properties such as 2,5-diarylated thieno[3,4-*b*]pyrazines[50] since compounds **10a−c** showed near-IR light emission and high fluorescence quantum yields (Φ_{fl}) in solution, up to 79.5% (Figures S1−3).

In the last part of our work, we wanted to demonstrate the feasibility of our DA protocol in DESs to a real-case scenario by preparing two EDOT-containing organic molecules (**5l,m**, Scheme 6) previously described in the literature. Compound **5l** was reported in 2014[62] and successfully applied as a hole transport material (HTM) for perovskite solar cells (PSCs): the original synthesis (Scheme 6A) was based on a Suzuki− Miyaura cross-coupling between dibromide **11** and boronic acid **12**, which must be prepared in turn by electrophilic bromination of **1** and lithiation and transmetalation of **2l**, respectively, with an overall yield of 62%. When our optimized

Scheme 6. Syntheses of the Products 5l (A) and 5m (B) through the DA Reaction in DESs and Comparison with the Literature-Reported Protocols
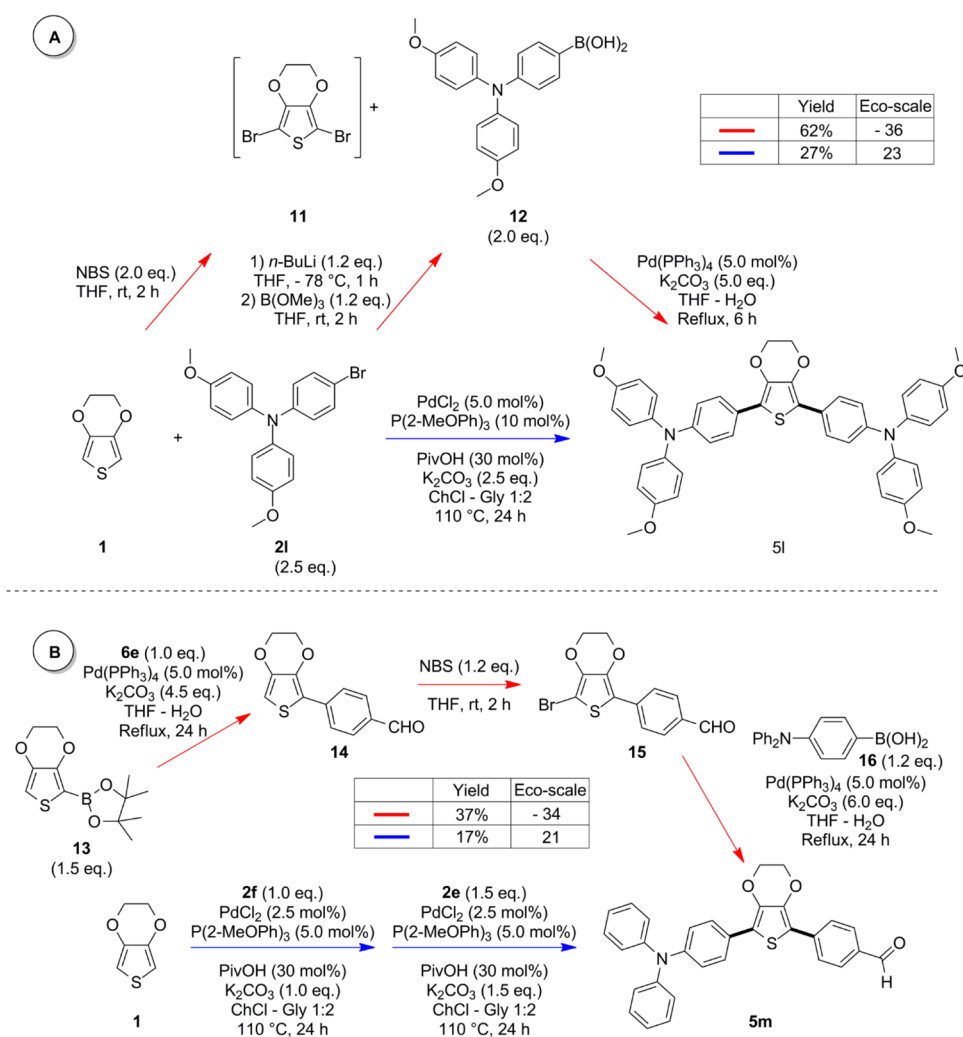
protocol was employed for the direct arylation of **1** with **2l**, without any further adjustment to the conditions, compound **5l** was isolated in 27% yield. Although such value was lower than that reported in the literature, the synthesis was significantly shortened (one step vs three steps) and the employment of a toxic and flammable solvent such as THF was avoided. As a result, a comparison of the Eco-scale values was in favor of the DA reaction in DESs (23 vs −36) due to the lower number of chromatographic purifications and the possibility of avoiding the use of polar organometallics like *n*-butyllithium.

The second EDOT-containing molecule selected from the literature[63] was **5m** (Scheme 6B), the last precursor of a metal-free photosensitizer for dye-sensitized solar cells (DSSCs). The original three-step synthesis featured a first Suzuki−Miyaura reaction between commercially available bromide **2e** and boronic ester **13**, followed by an electrophilic bromination of the resulting aldehyde **14**, and then, a second Suzuki−Miyaura coupling with boronic acid **16** to achieve the desired advanced intermediate **5m** in 37% yield overall.

Unlike the previous compounds, **5m** required the sequential arylation of **1** with two different bromides (**2e,f**) to obtain a nonsymmetrical D-π-A product. For this reason, we made small modifications to the general procedure, adjusting the

amount of both bromides and the base, and we investigated the effect of the order of addition of the bromides on the final yield. The best result was obtained by reacting EDOT first with the electron-rich bromide **2f** and then, without isolating any intermediate, with the electron-poor bromide **2e**, simply by adding all of the reagents in the same DES. The desired product **5m** could thus be isolated in a 17% yield, which is comparable to previously reported one-pot asymmetrical double arylation reactions in conventional solvents.[48] Again, despite a lower yield than that reported in the literature, the calculated Eco-scale for the DA-based synthesis (21) in DESs was much higher than that calculated for the literature procedure (−34), mainly because of the reduction of waste stemming from chromatographic columns and the substitution of toxic and flammable reagents. In our opinion, this last example is particularly interesting since it demonstrated the possibility to accomplish a *one-pot* double functionalization of symmetric substrates with different arenes, paving the way for the preparation of D-π-A compounds through direct arylation in DESs.

■ CONCLUSIONS

The direct arylation of a series of thienyl-substituted compounds like ethylenedioxythiophene and thieno[3,4-*b*]-

pyrazines with (hetero)aromatic bromides in DESs was investigated. It was found that the reaction can be performed in a biocompatible choline chloride/glycerol (1:2) mixture under air, using affordable reagents, such as $PdCl_2$ and K_2CO_3, and tolerated the introduction of several functional groups like ketones, aldehydes, nitriles, carboxylic acids, esters, and nitro groups. Yields up to 95%, with a catalyst loading as low as 1 mol %, were obtained, in particular, when electron-poor aromatic bromides were employed. The optimized DA protocol in DESs was also successfully employed for the preparation of conjugated symmetric and nonsymmetrical molecules with applications in the photovoltaic field. The sustainability of DA in DES was evaluated for the first time through calculations of the most common green metrics, E-factor and Eco-scale, which ranked most of the syntheses as "*excellent*"/"*acceptable*" according to the original paper of Van Aken et al.[66] or showed an improvement in comparison with the literature. This protocol expanded the reaction scope of the DA reaction in DESs and filled the gap between direct arylation reactions and other more consolidated cross-coupling procedures in neoteric and sustainable solvents.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.1c08466.

> Experimental section: general remarks; optimization of the reaction conditions for the direct arylation in DES; optimized general procedure for the direct arylation protocol and general workup procedures; preparation procedures, characterization, and green chemistry metrics; UV−vis and fluorescence spectra; and copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Lorenzo Zani − *Institute of Chemistry of Organometallic Compounds (CNR-ICCOM), Sesto Fiorentino 50019, Italy;* ⓞ orcid.org/0000-0003-0621-2648; Email: lorenzo.zani@iccom.cnr.it

Alessio Dessì − *Institute of Chemistry of Organometallic Compounds (CNR-ICCOM), Sesto Fiorentino 50019, Italy;* ⓞ orcid.org/0000-0002-2813-2369; Email: alessio.dessi@iccom.cnr.it

Authors

Francesco D'Amico − *Institute of Chemistry of Organometallic Compounds (CNR-ICCOM), Sesto Fiorentino 50019, Italy; Department of Biotechnology, Chemistry and Pharmacy, University of Siena, Siena 53100, Italy*

Costanza Papucci − *Institute of Chemistry of Organometallic Compounds (CNR-ICCOM), Sesto Fiorentino 50019, Italy; Department of Chemistry "U. Schiff", University of Florence, Sesto Fiorentino 50019, Italy*

Daniele Franchi − *Institute of Chemistry of Organometallic Compounds (CNR-ICCOM), Sesto Fiorentino 50019, Italy*

Gianna Reginato − *Institute of Chemistry of Organometallic Compounds (CNR-ICCOM), Sesto Fiorentino 50019, Italy;* ⓞ orcid.org/0000-0002-7712-3426

Massimo Calamante − *Institute of Chemistry of Organometallic Compounds (CNR-ICCOM), Sesto*

Fiorentino 50019, Italy; Department of Chemistry "U. Schiff", University of Florence, Sesto Fiorentino 50019, Italy

Alessandro Mordini − *Institute of Chemistry of Organometallic Compounds (CNR-ICCOM), Sesto Fiorentino 50019, Italy; Department of Chemistry "U. Schiff", University of Florence, Sesto Fiorentino 50019, Italy*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acssuschemeng.1c08466

Author Contributions

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Notes

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■ DEDICATION

Dedicated to the memory of Professor Victor Snieckus.

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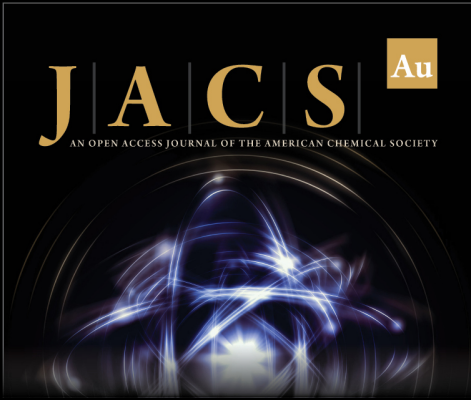
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