Journal Name

Efficient organic semiconductors synthesis by Suzuki-Miyaura coupling in aromatic micellar medium[†]

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Micellar catalysis enable carrying out Suzuki-Miyaura couplings in water under exceptionally mild conditions. Extension of such protocol to the sustainable synthesis of highly conjugated, poorly soluble materials like [1]benzothieno[3,2-b][1]benzothiophene (BTBT) requires redesigning of the surfactants employed. The here reported new naphthalenediimide containing amphiphilic derivative, PiNap-750M, features unprecedented performances in the preparation of this and other relevant classes of organic semiconductors in water and at room temperature.

Introduction

Sustainability is rapidly becoming a key priority in synthetic chemistry. In this respect, the reduction of organic solvents consumption and energy intake of reactions represents a critical aspect.[1,2] The development of synthetic protocols exploiting interface rich aqueous systems the like of micellar solutions, emulsions, microemulsions and vesicles is giving a tremendous contribution to both issues.[3–5] The underlying catalytic effects enable faster reaction kinetics at room temperature, along with a drastic reduction of the organic solvents employed. The generality of the approach is endorsed by the everyday increasing number of reactions documented to be particularly efficient when carried in microheterogeneous environment. To name but a few, Suzuki-Miyaura, Heck, Buchwald-Hartwig, Stille, olefin metathesis, Sonogashira and even photoredox couplings are all well documented.[5–9]

The selection of the most suitable surfactant is key for the success of microheterogeneous, interface rich reactions. Literature reports a vast number of performing derivatives, ranging from inexpensive industrial surfactants to specifically designed amphiphiles, frequently derived from naturally occurring building
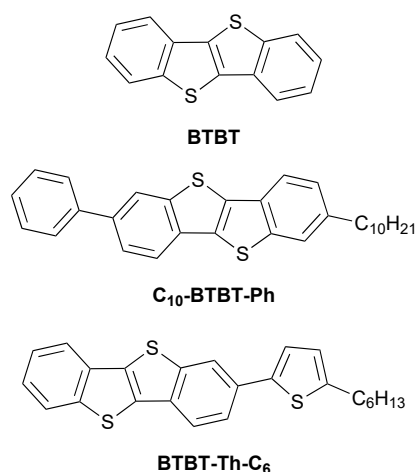

Fig. 1 Structure of BTBT and two relevant structurally related molecular semiconductors

blocks.[10] Some of them have a wide applicability and ensure high performances at very low catalyst loading. The vitamin E containing polyethoxylated derivatives introduced by the Lipshutz group certainly play a particularly relevant role.[6,11] Industrial surfactants can also be fruitfully employed. Amongst them, Kolliphor EL (K-EL) proved to be a viable and cheap solution to carry out both Suzuki-Miyaura (SM) and Buchwald-Hartwig (BH) couplings on aromatic and heteroaromatic derivatives under mild conditions, in high yield and under standard laboratory atmosphere.[12,13] However, complete generality remains to be demonstrated, as surfactant enforced reactions can show unexpected behaviour when compared to homogeneous media. Slight changes in the way reactions are performed (mixing speed and method) can significantly alter results.[14] The use

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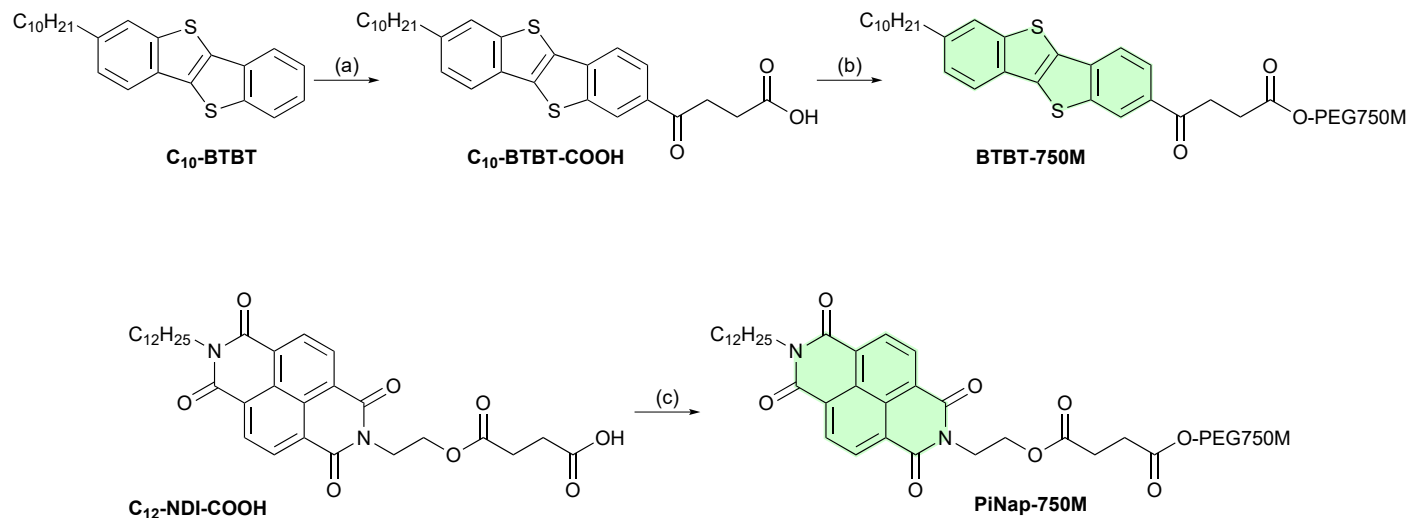
Scheme 1 Structures of designer surfactants BTBT-750M and PiNap-750M, and their syntheses starting from known precursors. (a) succinic anhydride, aluminum trichloride in DCM, −83 °C to r.t., 8 h, 19.7 %. (b) PEG-750M, PTSA in toluene, reflux 2 h, 85.2 %. (c) PEG-750M, Boc_2O, DMAP in DCM, r.t., six days, 72.1 %. Details about synthesis of $C_{10}-BTBT$ and $C_{12}-NDI-COOH$ precursors are reported in the ESI[†].

of surfactants preferentially stabilizing colloidal dispersions of products versus reagents can also impact on conversion.[15] The very same change in the nature of a formulation (i.e. from emulsion to dispersion/suspension) can affect conversion and yield.[16] The synthesis of highly conjugated, rigid and poorly soluble organic semiconductors is particularly challenging in the above-mentioned respects. Indeed, the field of plastic electronics is on the verge of the "Lab to Fab" transition and thus in dire need for ways to improve the sustainability of the synthetic processes employed, so far often relying on toxic organic solvents and hazardous chemicals with E-factors routinely exceeding 1000.[17] The use of established surfactants enables the preparation in water of model materials,[15] yet more elaborate substrates having consolidated applications require the use of organic cosolvents.[18] Such a strategy is generally successful in case of poorly dispersible chemicals.[16,19] Amongst the most prominent classes of small molecule organic semiconductors, [1]benzothieno[3,2-b][1]benzothiophene (BTBT) derivatives offer particularly ambitious synthetic targets (Figure 1). Truly, such derivatives are known to be particularly performing as p-type semiconductors precisely because of their strong tendency to form tightly packed, poorly soluble crystalline structures where cohesive forces are dominated by $\pi-\pi$ interactions.[20–22] Surfactants specifically designed to compete with such specific interactions could provide unique performances when applied to the manufacturing of BTBT and other application relevant molecular semiconductors. We thus synthesized two new amphiphiles on the basis of this design paradigm, PiNap-750M and BTBT-750M, both featuring extensive conjugated portions in the hydrophobic compartment, specifically introduced in order to establish $\pi-\pi$ interactions with organic semiconductors building blocks (Scheme 1). In this respect, it has already been demonstrated how surfactants possessing aromatic residues in the lipophilic portion can be successfully applied to obtain aqueous dispersions of materials having extended π-conjugation

and strong tendency to aggregation (like graphite, or carbon nanotubes);[23,24] along with proof-of-concept results on Suzuki-Miyaura couplings in aromatic micellar medium on very simple biphenyl derivatives.[25]

We will show how the exceptional dispersant capabilities of PiNap-750M towards π-extended derivatives enable carrying out micellar couplings in water alone, at room temperature and with remarkably short contact times, affording the target compounds with unprecedented high simplicity and sustainability.

Results and discussion

Amongst the various BTBT derivatives described in the literature, $C_{10}-BTBT-Ph$ and $BTBT-Th-C_6$ represent relevant synthetic targets (Figure 1). Indeed they are efficient molecular semiconductors with demonstrated applications in devices and surface science in general.[26,27] They also exemplify the most common elaborations of the BTBT core according to the late stage functionalization approach. Literature protocols for the preparation of $BTBT-Th-C_6$ and $C_{10}-BTBT-Ph$ require standard Stille and Suzuki-Miyaura couplings, respectively, starting from the corresponding BTBT brominated derivative and the appropriate organotin or arylboronic derivatives.[26,27] According to the generally higher sustainability of the SM over Stille reaction, we focused on the optimization of the former in both cases. Prior to move on the aforementioned targets, we studied the SM coupling of phenyboronic acid and 2-bromo-[1]benzothieno[3,2-b][1]benzothiophene (BTBT-Br) as a model reaction (see heading of Table 1). We selected K-EL as the surfactant according to our previous experience with conjugated derivatives: K-EL is very cheap, performs comparably to efficient designer surfactants and enables carrying out SM reactions under standard laboratory conditions.[12] Entry 1 of Table 1 shows that the use of a 2 wt% K-EL water solution as the reaction medium gives very poor results: the yield is 26 % after 6 h at r.t.. Prolonging the reaction
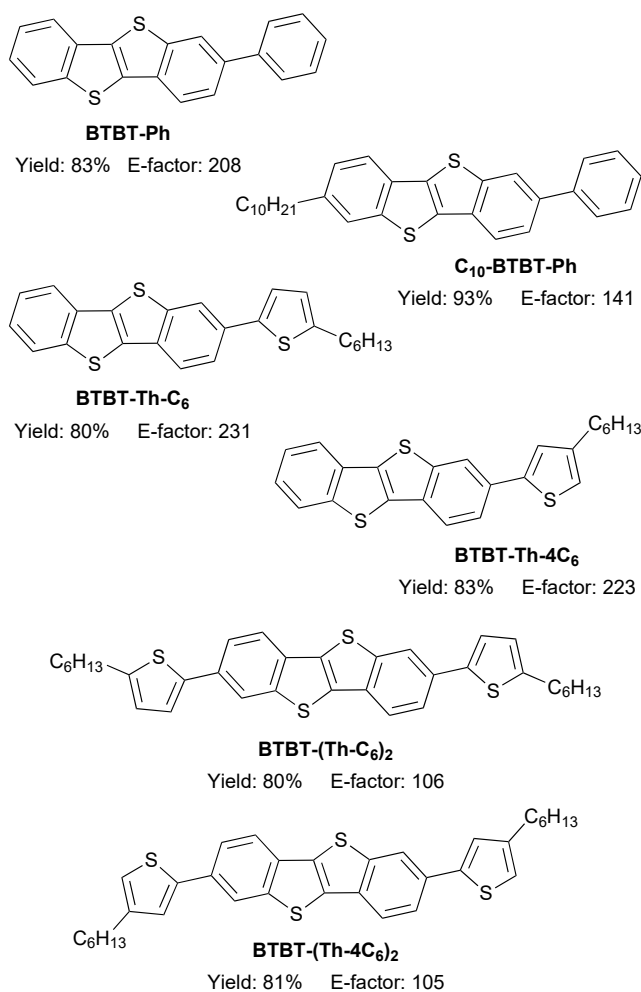
BTBT-Ph
Yield: 83% E-factor: 208

C$_{10}$-BTBT-Ph
Yield: 93%   E-factor: 141

BTBT-Th-C$_6$
Yield: 80%   E-factor: 231

BTBT-Th-4C$_6$
Yield: 83%   E-factor: 223

BTBT-(Th-C$_6$)$_2$
Yield: 80%   E-factor: 106

BTBT-(Th-4C$_6$)$_2$
Yield: 81%   E-factor: 105

Fig. 2 BTBT coupling products, with yields and E-factors obtained under emulsion conditions.

time does not improve conversion. The use of a cosolvent, in full agreement with literature results under similar conditions,[16] dramatically improves the reaction. In the case of the water miscible THF, the reaction mixture remains in the micellar regime and the yield reaches 50 %, again after 6 h at r.t. (entry 2). In the case of toluene, with the reaction mixture turning into an emulsion, results are comparable at r.t. (entry 3), eventually achieving quantitative conversion and 90 % yield after chromatographic purification, when working at 80 °C for just 1 h and under standard laboratory environment (entry 4). This emulsion method can be extended to different BTBT derivatives (see Figure 2) with good to excellent yields and represents a huge step forward in comparison to literature reported conditions from the standpoint of both efficiency and sustainability (see ESI† for details on E-factors calculations). However, it still had a few weaknesses to qualify as truly green chemistry compliant: the use of toluene as the cosolvent and the requirement for a still somewhat prolonged heating, along with the need for chromatographic purification of the final products. Since toluene is not playing a direct role in promoting the couplings, but rather acting as a mixing aid to properly disperse all reagents, we concluded that tailor-designed surfactants

could take that role and possibly outperform it.

According to the formulation chemistry guidelines, surface active molecules achieve best results in dispersing a target phase when the lyophobic portion of the surfactant either resembles or in any case strongly interacts with the phase to be dispersed.[28] We decided to exploit such concepts by designing two conjugated designer surfactants featuring a BTBT and a naphthalenediimide (NDI) residues as the lyophobic portion and, in analogy with established literature on designer surfactants,[7] a PEG-succinate residue as the lyophilic one. In the first case, the BTBT-750M surfactant, the design is based on the affinity principle and the synthesis is straightforward. The first step requires reaction of the known precursor BTBT−C$_{10}$ and succinic anhydride in the presence of AlCl$_3$ to give the acid derivative C$_{10}$−BTBT−COOH, subsequently condensed with PEG-750M in the presence of PTSA in a standard Fischer esterification protocol. For PiNap-750M, the design was guided by the idea of further strengthening the π-stack interaction between surfactant and components of the reaction mixture by adding a donor-acceptor contribution. Indeed, the NDI unit is one of the most established structural motifs in the preparation of electron-deficient organic semiconductors.[29–31] The opposite is true for the BTBT core, commonplace amongst electron rich semiconductors. The resulting donor-acceptor π-stack interaction was intended to help achieving a stable formulation at all stages of the reaction. The choice of the NDI core also came from synthetic reasons: high yield and facile elaborations of the NDI core leading to unsymmetrically substituted derivatives are very well documented in the literature.[32,33] PiNap-750M was thus synthesized from the unsymmetrical derivative C$_{12}$−NDI−COOH (prepared following literature conditions[32,33]), which was condensed with PEG-750M using Boc$_2$O in the presence of DMAP,[34] as the Fischer esterification protocol did not allow to obtain the product. Further details pertaining to the π-surfactants syntheses are reported in the ESI†. DLS measurements (see figure S1 and S2 of ESI†) suggest that BTBT-750M mostly self assembles into micelles having a 15 nm average diameter, while the behavior of PiNap-750M is more complex, showing the formation of several distinct populations of objects having average hydrodynamic diameter of 60, 1100 and 4300 nm. Whilst the smallest colloids are possibly wormlike micelles, the larger objects are aggregates having different nuclearity. The use of such designer surfactants in the place of K-EL helped dramatically the efficiency of the SM couplings. As it is shown in Table 1, if the test coupling reaction between BTBT-Br and phenylboronic acid is carried out in 2 wt% BTBT-750M at room temperature and under standard laboratory environment, BTBT-Ph can be isolated in 73 % yield after chromatographic purification (entry 5) as opposite to the mere 26 % obtained when working with K-EL under the same conditions. If the reaction is carried out under nitrogen atmosphere and with degassed water, the yield becomes quantitative, provided that the reaction time is prolonged to 48 h (entry 7). In this case, as opposite to what we routinely observe with K-EL, the catalyst is slowly poisoned by environmental oxygen, as it is actually the rule for most surfactants, designer or not. The same reaction carried out in a 2 wt% solution of PiNap-750M gives even more striking results. The behav-

Table 1 Micellar catalyzed coupling of phenylboronic acid and BTBT-Br.
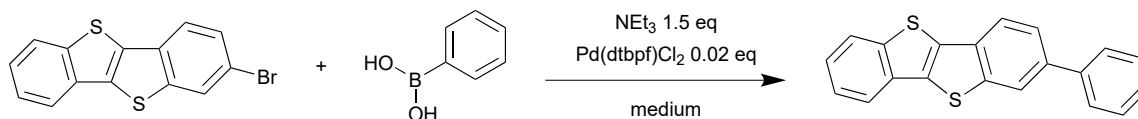
Entry	Medium	Atm.	T (°C)	Time (h)	Yield (%)
1	K-EL 2 wt%	air	25	6	26
2	K-EL 2 wt%-THF 9:1 v/v	air	25	6	50
3	K-EL 2 wt%-toluene 9:1 v/v	air	25	6	45
4	K-EL 2 wt%-toluene 9:1 v/v	air	80	1	90
5	BTBT-750M 2 wt%	air	25	24	73
6	PiNap-750M 2 wt%	air	25	1	78
7	BTBT-750M 2 wt%	N_2	25	48	97
8	PiNap-750M 2 wt%	N_2	25	1	97
9[a]	PiNap-750M 2 wt%	N_2	25	12	97
10[b]	PiNap-750M 2 wt%	N_2	25	24	67

[a] 0.004 eq. of catalyst were used.
[b] 0.002 eq. of catalyst were used. NMR conversion is reported instead of yield.

Table 2 Results of couplings carried out in PiNap-750M 2 wt% solutions with corresponding E factors. A comparison of current E-factors with those from literature procedures is reported where available (see ESI[†] for calculation details).

Entry	Product	Ar−Br	Atm.	Time (h)	Yield (%)	E Factor calc. (lit.)
1	BTBT−Ph	BTBT−Br	N_2	1	97	46.6 (1556)
2	C_{10}−BTBT−Ph	C_{10}−BTBT−Br	N_2	1	94	33.4 (787)
3	BTBT−Th−C_6	BTBT−Br	N_2	1	91	39.2 (1117)
4	BTBT−Th−$4C_6$	BTBT−Br	N_2	1	93	38.4 (−)

ior of such surfactant is peculiar as the reaction mixture assumes a blue colour (Figure S3 of the ESI[†]), that is characteristic of the co-presence of NEt_3, PiNap-750M and the catalyst. If the reaction is run under standard laboratory atmosphere, the colour fades away in less than 1 h and the isolated yield of BTBT-Ph reaches 78 % (entry 6). Conversely, if the reaction is carefully deoxygenated, the blue colour remains visible and the reaction goes smoothly to quantitative conversion and yield in 1 h (entry 8). Under otherwise identical conditions, we repeated the reaction reducing the amount of catalyst to 0.004 and 0.002 equivalents in order to evaluate the optimal required catalyst loading. Reaction reached completion only in the first case (Entry 9), but required 12 h. In the latter case conversion was not complete even after 24 h and the conversion was 67 % (entry 10). Encouraged, we repeated the syntheses of C_{10}−BTBT−Ph, BTBT−Th−C_6 and BTBT−Th−$4C_6$ employing degassed 2 wt% dispersion of PiNap-750M, 2 mol% catalyst, no cosolvent and no heating (Table 2). In all of the cases the reaction was complete in less than 1 h, and after dilution of the reaction mixture with ethanol the pure product could be obtained simply by filtration, with isolated yields of 94 %, 91 % and 93 % respectively. E-factors for the coupling reactions (calculated including water and the purification steps, Table 2) are in the 33-47 range, with a two order of magnitude improvement over standard literature procedures. Such remarkably improved performances over the BTBT-750M surfactant could be correlated to two different factors. The first one implies the establishment of stabilizing NDI-BTBT donor-acceptor interactions improving the capability of PiNap-750M to efficiently disperse electron rich reagents. This explanation implies that PiNap-750M ex-

ceptional performances should be more prominent in the case of electron rich bromides. The second one is on the contrary substrate independent. It is based upon the observation of the blue coloration assumed by the reaction mixture only in the case of the co-presence of NEt_3, PiNap-750M and Pd catalyst and never observed for any one of the other surfactants we employed in this and previous studies. PiNap-750M could be involved as a ligand in the formation of a new Pd(0) complex having different (in this case improved) efficiency in promoting SM couplings. An analogous colour change is observed upon addition of NEt_3 to a CH_3CN solution of PiNap-750M/Pd-catalyst under argon atmosphere. Figure S4 of the ESI[†] shows the absorption spectra of a CH_3CN solution of $Pd(dtbpf)Cl_2$ before and after the addition of NEt_3, highlighting the formation of a new broad absorption band peaking at 590 nm and reminiscent of the Metal to Ligand Charge Transfer band of the popular Pd(0) complex $Pd_2(dba)_3$.[35] This behavior and the oxygen sensitivity of the blue species generated by the reduction of the $Pd(dtbpf)Cl_2$ are circumstantial evidence that this could be the case. This second explanation does not imply any selectivity towards electron rich bromides: all SM reactions should be improved in the presence of PiNap-750M.

In the absence of further evidences, we challenged PiNap-750M in additional SM couplings on both electron-rich and electron-poor bromides. Scheme 2 shows the results obtained for the coupling of 9,10-dibromoanthracene, 4,7-dibromo-2,1,3-benzothiadiazole, N,N′-bis(2-ethylhexyl)-6,6′-dibromoisoindigo and N,N′-bis(n-octyl)-1,7-dibromo-perylene-3,4:9,10-bis(dicarboximide). Rather remarkably, the use of PiNap-750M allows to synthesize derivatives **1**, **2**, **3** and **4** in es-
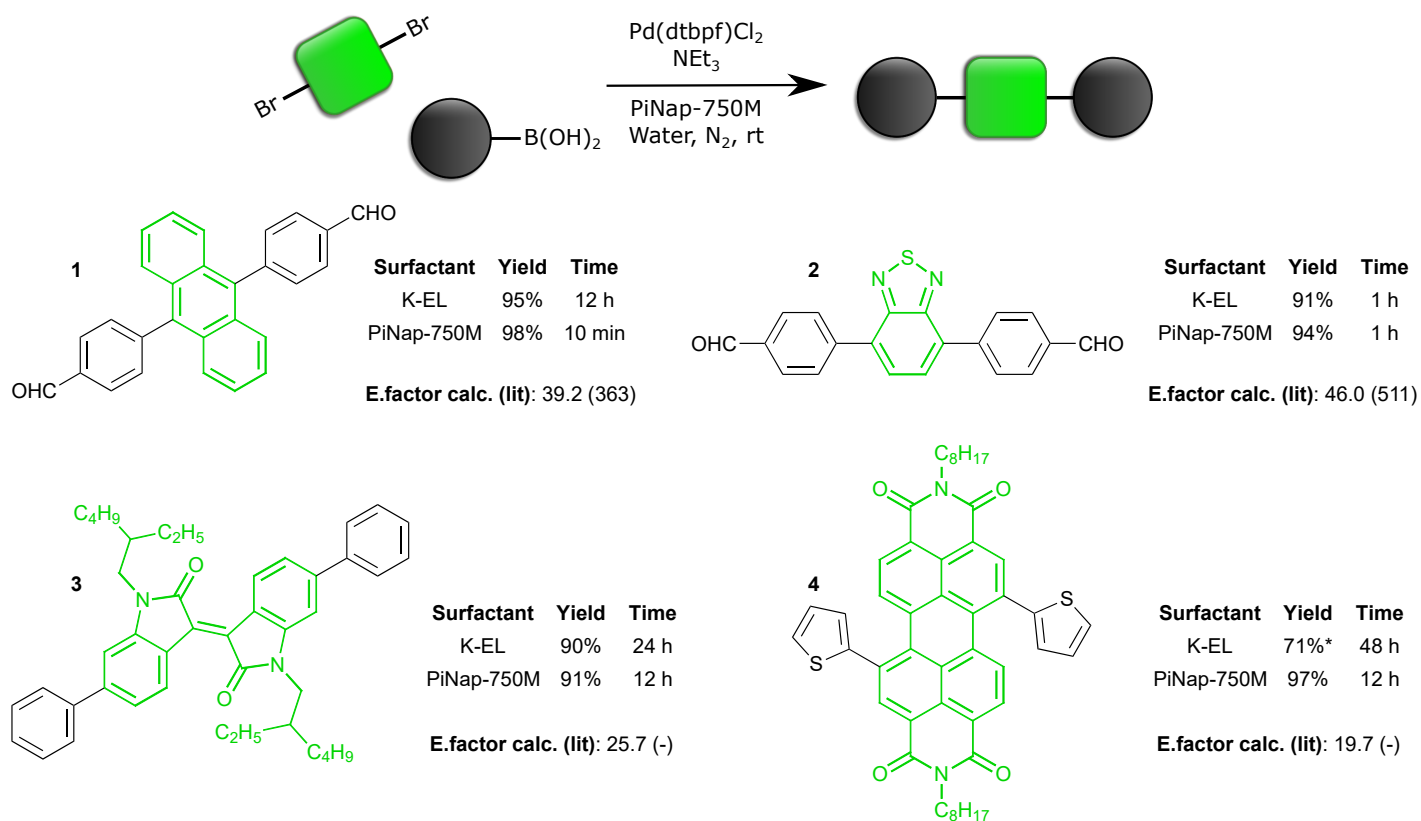
Scheme 2 Couplings of brominated precursors (in green) and arylboronic acids (in black) performed in a 2 wt% PiNap-750M solution in deionized water, and their E-factor (comparison with E-factor from literature procedures is reported where available, see ESI† for calculation details). *Conversion as estimated by ^{1}H NMR.

sentially quantitative yield at room temperature, without added cosolvent and in shorter reaction times than those needed for the same reaction to occur in K-EL. Again, E-factors were improved by more than one order of magnitude with respect to reported literature procedures.

On the basis of such evidences, PiNap-750M is extremely efficient, regardless to the electron poor or electron rich nature of the aromatic core of the starting bromide. Although these results are consistent with the formation of a Pd/PiNap-750M complex, they do not provide a clear-cut evidence in support of such an interpretation neither a mechanistic insight into its role in enhancing the catalytic activity. Further experimental and computational studies are under way to further substantiate our educated guessing.

Conclusions

We introduce two new designer surfactants, BTBT-750M and PiNap-750M, specifically designed to promote SM reactions on organic semiconductors, of interest for printed electronic applications, in water. The use of such surfactants, particularly of PiNap-750M, enables carrying out reactions in the absence of a cosolvent, at room temperature and with unprecedented short reaction times. As a case study, relevant BTBT derivatives are obtained with dramatically improved E-factors with respect to literature procedures. Preliminary results on bromides of other organic semiconductors support generality of the benefits conveyed by the use of PiNap-750M in the manufacturing of printed electronic strategic materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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