Minimalistic β-sitosterol based designer surfactants for efficient cross-coupling in water

Tommaso Lorenzetto, Davide Frigatti, Fabrizio Fabris, Alessandro Scarso*

Università Ca' Foscari Venezia, Dipartimento di Scienze Molecolari e Nanosistemi, via Torino 155, 30172 Venezia, Italy

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ABSTRACT

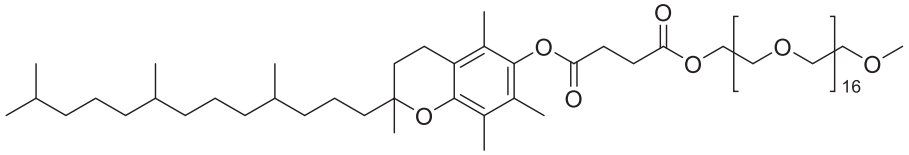
In this contribution, we report about the synthesis, the aggregation properties and their application in cross-coupling catalysis of two new designer surfactants comprising a rigid hydrophobic portion based on β-sitosterol directly linked by an etheric bond to methyl polyoxoethylene chains. The proposed amphiphilic compounds represent a minimalistic approach with respect to the Lipshutz's third generation designer surfactant **Nok.** The amphiphiles displayed improved chemical stability, shorter synthesis, and good properties in Pd-catalyzed cross-coupling reactions in water under mild conditions, as compared with other neutral commercially available surfactants.

1. Introduction

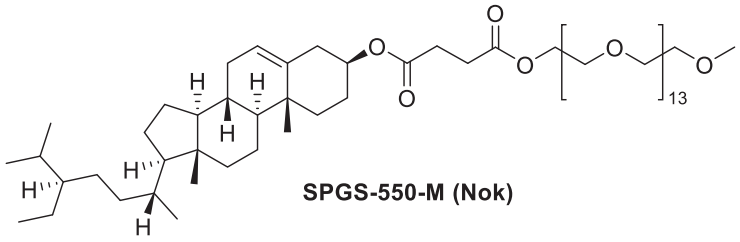
Catalysis in water is nowadays a real green alternative to catalysis in organic polar aprotic media, in fact also several pharmaceutical companies are exploring and implementing the use of water as a medium to run large scale reactions [1]. The inability of water to solubilize organic compounds and metal catalysts is not always a problem, rather it can be an advantage as recently reviewed in a paper concerning aquachemistry that relies on neither cosolvents nor surfactants. In the paper catalytic reactions promoted by water as solvent are discussed even though the reactions are not homogeneous and several phases are present [2]. Since every combination of reagents and catalysts provide different results when considering the same reaction run in pure water, the use of surfactants as additives emerged as a real general alternative for catalytic reactions in this solvent. Micellar catalysis is one very effective approach to overcome the issues highlighted by the Principles of Green Chemistry [3]. In particular these self-aggregating systems improve the solubilization of non-polar organic reactants and catalysts leading to increased local concentration responsible for the acceleration of the rate of the reactions. The anisotropic structure of micelles enhance selectivities due to the ordered nanoenvironment. Moreover, micelles favor the recycling of the catalyst, especially for reactions involving products that are more hydrophobic than the reagents [4]. In almost two decades the field of transition metal catalysis in micellar media [5–7] has been revolutionized in particular by the advent of designer surfactants introduced several years ago by Lipshutz [8] as new amphiphilic molecules specifically designed and developed for catalytic applications in water [9–11]. Some designer surfactants like **TPGS-750-M** [12], **Nok** [13] and **PS-750-M** [14] (Chart 1) are now commercially available thanks to their versatility and fruitful application into a wide range of transition metal catalyzed reactions. In the recent years many other new designer surfactants have been proposed [15] based on different hydrophobic and hydrophilic portions with the aim to improve the catalytic performance, but also focusing the attention on the overall sustainability of the synthesis of the surfactant and its downstream degradation. Very recently Lipshutz proposed a new surfactant called **TPG-lite** [16] characterized by a shorter and more straightforward synthesis, more robust toward hydrolysis of the ester unit present in the structure, with lower molecular weight and potential reduction of the downstream processing compared to **TPGS-750-M**.

In the present contribution we report the synthesis, the aggregation properties and the application in cross coupling reactions and recycling for metathesis reactions of two new designer surfactants **Sito-350-M** and **Sito-750-M** (Chart 1) bearing a β-sitosterol based hydrophobic portion directly connected to methyl-polyethylene glycol (MPEG) neutral hydrophilic chains of 7 and 14 oxyethylene units, respectively. Such new surfactants represent a "lite" version of the commercially available surfactant **Nok** in which a succinic spacer is present in between the β-sitosterol and MPEG-550 hydrophilic unit bearing 13 oxyethylene units.

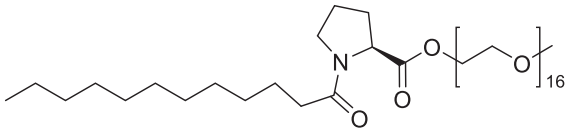
* Corresponding author.
E-mail address: alesca@unive.it (A. Scarso).



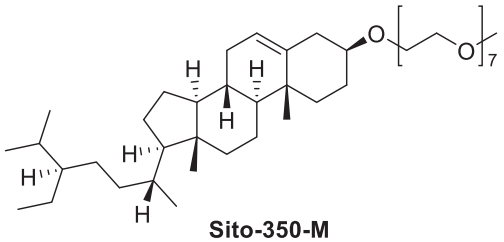
TPGS-750-M



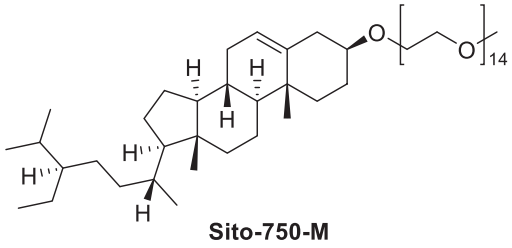
SPGS-550-M (Nok)



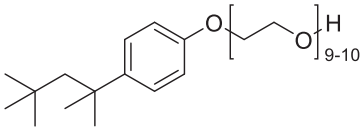
PS-750-M



Sito-350-M



Sito-750-M



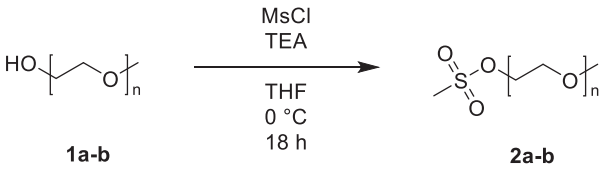
Triton X-100

Chart 1. Structure of the non-ionic surfactants TPGS-750-M, Nok, PS-750-M, Sito-350-M, Sito-750-M and Triton X-100.

2. Results and discussion

2.1. Synthesis of the new designer surfactants sito-350-m and sito-750-m

The design of the new surfactants was focused on the removal of the succinic ester linker in order to i) obtain a more straightforward synthesis, ii) improve the chemical stability in different and extreme pH conditions which is important for future potential applications in telescopic reactions and iii) obtain a completely rigid chiral apolar portion for potential future applications in stereoselective reactions. The synthesis of **Sito-350-M** and **Sito-750-M** involved the introduction of methyl-polyethylene glycol (MPEG) tails in which the terminal primary alcohol of MPEG-350 and



n = 7 (**1a**, **2a**); 14 (**1b**, **2b**)

Scheme 1. Synthesis of methanesulfonated MPEG-350 2a and MPEG-750 2b.

Table 1
Comparison between the Hydrophilic Lipophilic Balance (HLB) of the surfactants used and presented in this study.

Surfactant	HLB value
TPGS-750-M	12
SPGS-550-M (Nok)	11
Triton X-100	14
PS-750-M	14
Sito-350-M	9
Sito-750-M	12

MPEG-750 was transformed into a good leaving group by treatment with methanesulfonyl chloride and triethylamine in cold THF (Scheme 1) [17]. The methanesulfonated MPEG products were obtained in good yields and gram quantities (**2a**: 5.97 g; 95% yield; **2b**: 8.20 g, 65% yield) after a work-up procedure to neutralize the excess of methanesulfonyl chloride (Scheme 2).

In order to link the obtained products to the β-sitosterol **3**, the latter was transformed into a good nucleophile by reaction with sodium hydride in anhydrous toluene. A solution of **2a-b** in anhydrous toluene was then added dropwise to the mixture and vigorously stirred at 50 °C enabling to obtain the desired products **Sito-350-M** and **Sito-750-M** in grams scale with 37% and 59% isolated yields, respectively.

It is worth to note that the molecular weight distribution of the starting reagents **1a** and **1b** as determined by ESI MS analyses evidenced the presence of a mixture of MPEG compounds with a broad distribution of oxyethylene units. This was directly reflected into the molecular weight distribution of the products **Sito-350-M** and **Sito-750-M** for which an average molecular weight of 693.06 g/mol and 1045.49 g/mol was determined, respectively.

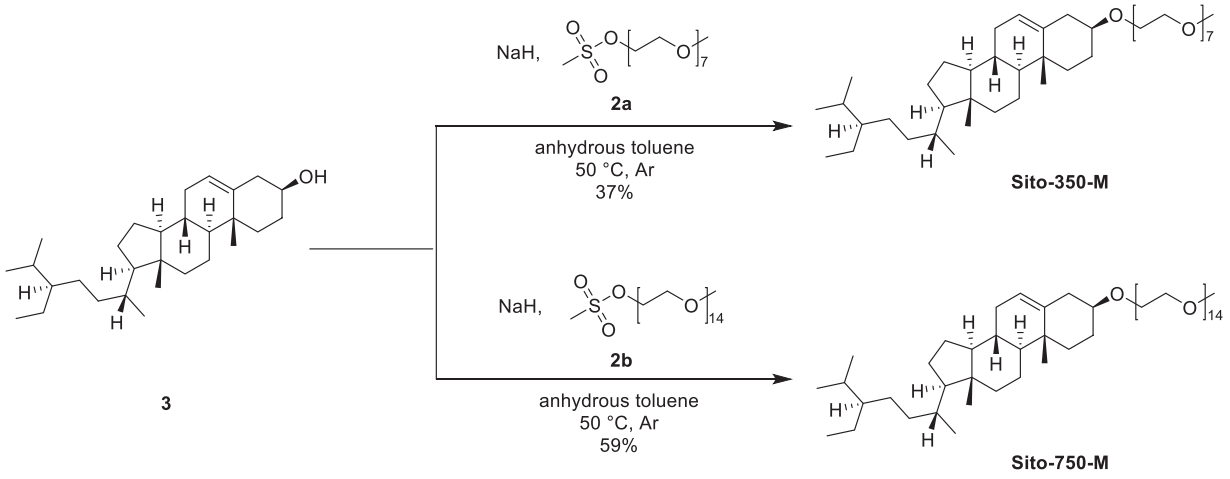
2.2. Aggregation of sito-350-m and sito-750-m in water

From a theoretical point of view, both **Sito-350-M** and **Sito-750-M** display a Hydrophilic Lipophilic Balance value in line with those of the other surfactants considered in this study (Table 1). The lower HLB value of **Sito-350-M** originates from the shorter hydrophilic tail in proportion to the entire structure of the molecule. The value is consistent with those obtained for **SPGS-550-M (Nok)** and **Sito-750-M**, that possess longer hydrophilic polyoxyethylene chains leading to higher HLB values. All amphiphiles considered are categorised as "oil in water emulsifiers", according to Griffin's classification. However, these values are obtained from calculations that consider the relative dimension of the hydrophilic moiety of the amphiphiles, but does not take into account the shape, hindrance or electronic density of the apolar portion of the molecules. For this reason, performance of the single surfactant may vary considerably from other with similar HLB values and therefore every case has to be considered specifically.

Regarding **Sito-350-M** and **Sito-750-M**, both compounds showed to be soluble in water for concentrations up to about 14 mM. The ^{1}H NMR spectra of both species in deuterium oxide clearly showed sharp resonances for the MPEG side chains, while the β-sitosterol portion of the molecules led only to very large undefined resonances in the range 2.4–0.5 ppm (Fig. 1). This is a clear indication of the formation of micellar aggregates in solution. To ascertain the aggregation properties of the two surfactants in water, we registered a series of ^{1}H NMR spectra of the amphiphiles at variable concentrations in deuterium oxide, monitoring the change in the chemical shifts of the PEG units of the compounds as function of the inverse of the concentration in solution [18]. Even though the chemical shift changes were rather small, from the plots reported in Fig. 2 it was unambiguously determined the presence of discontinuity in the chemical shift, from which the c.m.c. for **Sito-350-M** was determined to be 7.3 mM (corresponding to 0.05% wt.) and for **Sito-750-M** the c.m.c. value was 7.8 mM (corresponding to 0.04% wt.). Despite the structure of the amphiphiles is similar, the small increase in c.m.c. value for the longer surfactant is justified by the presence in **Sito-750-M** of the longer hydrophilic MPEG chain that overall decrease its lipophilicity [19].

2.3. Application of the new designer surfactant in micellar catalysis

The properties of the two new designer surfactants under micellar catalysis conditions were evaluated in a series of Pd-catalyzed Suzuki-Miyaura cross-coupling reactions using the neu-



Scheme 2. Synthesis of the Sito-350-M and Sito-750-M.

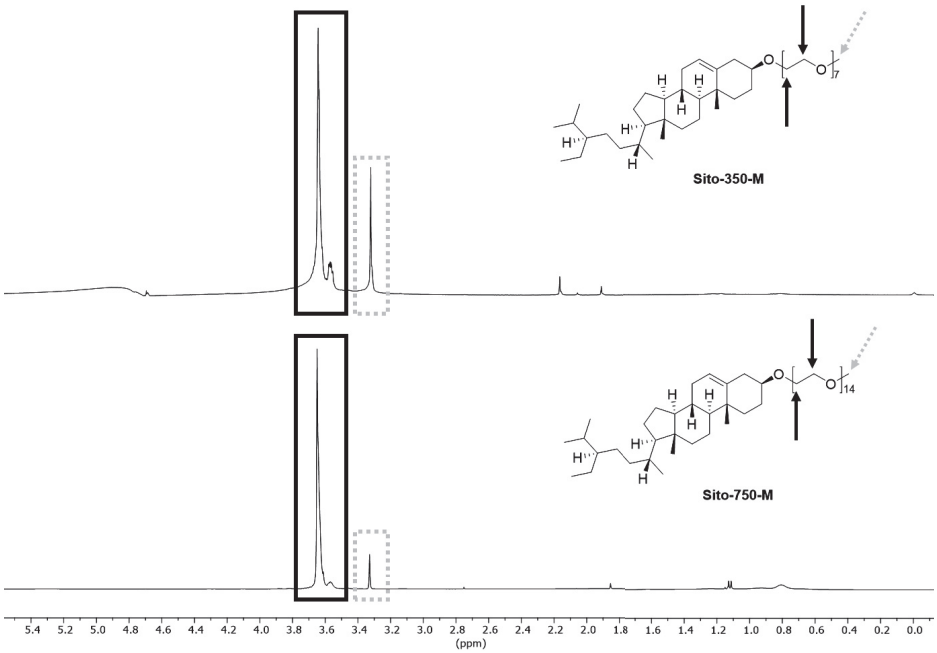


Fig. 1. ^{1}H NMR spectra of Sito-350-M 14 mM (bottom) and Sito-750-M 14 mM (top) in D_2O. The signals of the protons belonging to the polyoxyethylene chain has been highlighted. The signal of the solvent has been supressed. The resonances of the β-sitosterol moiety are really broad in the right part of the spectra.

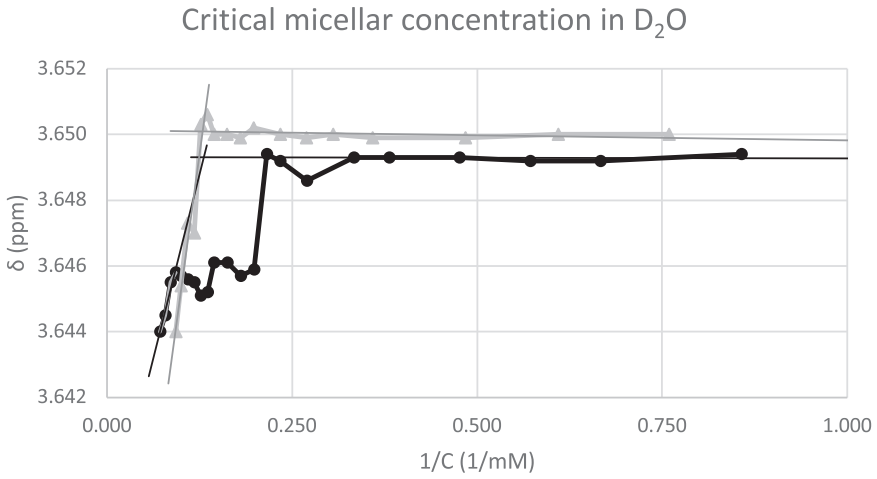


Fig. 2. Plot of the chemical shift of the oxyethylene H atoms of Sito-350-M (black circles) and Sito-750-M (gray triangles) as function of the inverse of the concentration and extrapolation of the c.m.c. values.

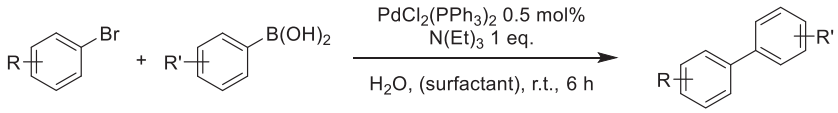
tral hydrophobic catalyst $PdCl_2(PPh_3)_2$ in just 0.5 mol% amount. The catalyst is not one of the most active for this class of cross coupling reactions, [20] and it was selected on purpose to emphasize the contribution of the surfactants to the outcome of the reactions. For the same reason we did not investigate the effect of the addition of co-solvents that is known to greatly improve the yields of the reactions [21]. **Sito-350-M** was tested using a 1% wt. solution in water which corresponds to 14.6 mM and **Sito-750-M** using a 2% wt. solution in water which corresponds to 19.5 mM, both values above the c.m.c. In order to contextualize the results obtained, we made other tests using two neutral surfactants bearing PEG hydrophilic side chains like **Triton X-100** 1% wt. corresponding to 15.6 mM above the c.m.c. of the surfactant, [22] and **TPGS-750-M** 2% wt. corresponding to 19.3 mM [23]. For the proposed new designer surfactants, the reaction mixture at the beginning appeared heterogeneous with yellow color and during the progress of the reaction it became more homogeneous and easy to stir with color change to dark.

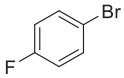
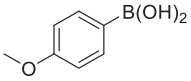
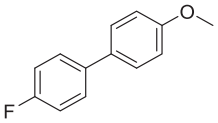
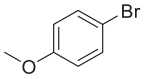
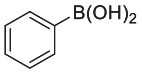
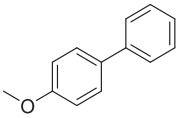
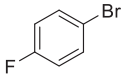
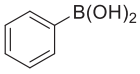
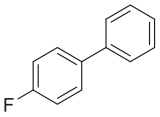
Results reported in Table 1 clearly show that in all the three reactions considered the yield observed using the two new surfactants were at least comparable or better than those observed with the two benchmark surfactants **Triton X-100** and **TPGS-750-M**. In particular, when using a more electron poor aryl bromide like 4-fluoro bromobenzene (Table 2, entries 1 and 3) yields were higher and similar results were observed with the four surfactants. Conversely, with the electron rich 4–methoxy bromobenzene (Table 2, entry 2) product yields were less similar among the surfactants, probably due to a more difficult oxidative addition step on the metal center of the catalyst.

Due to its better performance in these experiments, we further extended the application of **Sito-750-M** to a larger combination of substrates, in all cases comparing the results observed with the same reaction run with **Triton X-100** and **TPGS-750-M** (Table 3).

The results did not show a general trendline when comparing the different surfactants, in fact in some reactions the best one was clearly **TPGS-750-M** (Table 3, entries 3 and 4), in others it was **Tri-**

Table 2
Suzuki-Miyaura cross-coupling reactions between aryl bromides and aromatic boronic acid derivatives in water in the presence of **Triton X-100, TPGS-750-M, Sito-350-M** and **Sito-750-M**. a) Determined by NMR.



Entry	Aryl bromide	Boronic acid	Product	Triton X-100 Yield (%)[a]	TPGS-750-M Yield (%)[a]	Sito-350-M Yield (%)[a]	Sito-750-M Yield (%)[a]
1				88	88	76	90
2				49	35	60	52
3				66	60	65	63

ton X-100 (Table 3, entries 6 and 7) and in some cases **Sito-750-M** provided best results (Table 3, entries 1) or it was comparable to the best one (Table 3, entry 8). As a general trend, better yields were observed with more electron poor aryl bromides (Table 3, entries 7 and 6) and with more electron rich boronic acids (Table 3, entries 4 and 5). As frequently observed in micellar catalysis, it is clear that every combination of reagents and catalyst constitutes a different system in which the solubility and partition properties of all the species in water and in the apolar core of the micelles are crucial for the final effect of the catalytic reaction [4,9]. In this case only the surfactant acts as phase mediator between all the species involved in the reaction, therefore its chemical structure, aggregation and solubilization properties lead to differences that, as evidenced in Table 2, sometimes are rather large and not easily rationalizable. Overall, **Sito-750-M** turned out to be a possible alternative to known commercially available PEG based surfactants [23].

2.4. Recyclability of sito-750-m

Since one of the general advantages of micellar catalysis consists in the opportunity to recycle the micellar medium, we investigated this aspect in the intramolecular ring closing metathesis reaction of *N,N*-diallyl-4-methylbenzenesulfonamide **4** forming the corresponding cyclic product 1-tosyl-2,5-dihydro-1H-pyrrole **5** catalyzed by second generation Grubb's catalyst (Table 4) [24]. Exploiting the known low solubility of the polyoxyethylene moiety in diethyl ether, we used this solvent to recover the product at the end of the reaction while leaving the surfactant in the aqueous medium. Following known procedures, [12] we recycled the aqueous phase and added new reagents and catalyst for the next cycles. As comparison, we tested the recycling method also using **TPGS-750-M** (Table 4). As can be observed by the results, the activity of both the surfactants remained rather constant thorough the four cycles, with a slight increase in yield after the third cycle probably caused to the accumulation of the metal catalyst in the mixture. Even though **Sito-750-M** was intrinsically less efficient compared to **TPGS-750-M** for this specific reaction probably due to worse catalyst solubilization, the recycling procedure of the aqueous micellar medium was possible with both surfactants observing a rather constant yield in the corresponding cyclic product **5** even after overall four cycles.

3. Conclusions

In conclusion, herein we reported the synthesis, the aggregation properties, and the application in cross coupling reactions under micellar conditions of two new designer surfactants **Sito-350-M** and **Sito-750-M** which both represent a lite version of the commercially available surfactant **Nok**. The new surfactants, characterized by a direct ether bond between the β-sitosterol apolar unit and MPEG hydrophilic unit, were obtained in grams scale with just two synthetic steps with no chromatographic isolation in moderate to good overall yields. In water they showed strong aggregation properties with c.m.c. values 7–8 mM and promoted Suzuki Miyaura cross-coupling reactions under micellar conditions with activities and selectivities that were comparable to commercially available surfactants like **TPGS-750-M** and **Triton X-100**. The application of such new designer surfactants as chiral nanomicelles for stereoselective catalytic reactions in water is currently underway in our laboratory.

4. Experimental section

4.1. General methods

All the reactions were followed with TLC Polygram® Sil G/UV254, 0.25 mm thickness. ^{1}H NMR, ^{13}C NMR, and DOSY spectra were recorded with a Bruker Avance 300 and Ascend 400 spectrometers, working at 300–400 and 75–100 MHz respectively. ^{19}F NMR spectra were recorded with an Ascend 400 spectrometer, working at 376 MHz. Resonance frequencies are referred to tetramethylsilane. IR spectra were recorded with a Perkin Elmer Spectrum One spectrophotometer. Mass spectra were recorded on a Waters ZQ2000 spectrometer equipped with ESI Ion Polarity Positive source, with the following conditions: Set Nebuliser: 0.3 Bar, Focus Active Set Capillary: 4500 V, Set Dry Heater: 200 °C, Scan begins at 50 *m/z* and ends at 800 *m/z*, Set End Plate Offset: –500 V, Set Dry Gas: 3.5 L/min, Set Collision Cell RF: 2500.0 Vpp. A 1 mg/mL solution of sample in water was diluted 1:1000 into

Table 3
Suzuki-Miyaura cross-coupling reactions between aryl bromides and aromatic boronic acids in water with **Triton X-100, TPGS-750-M** and **Sito-750-M**. a) Determined by NMR.

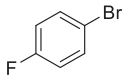
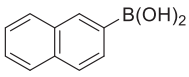
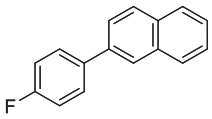
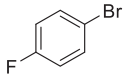
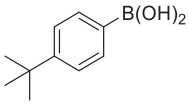
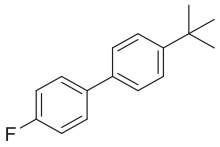
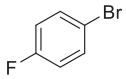
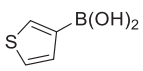
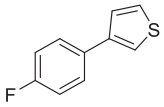
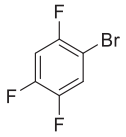
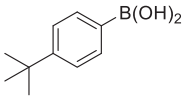
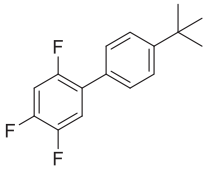
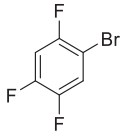
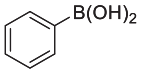
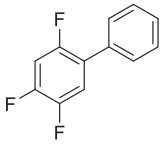
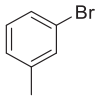
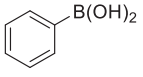
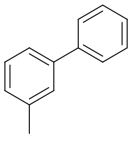
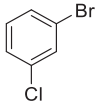
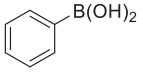
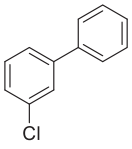
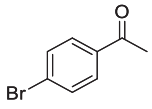
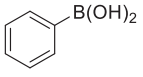
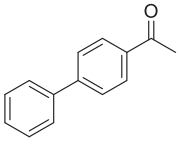
Entry	Aryl bromide	Boronic acid	Product	Triton X-100 Yield (%)[a]	TPGS-750-M Yield (%)[a]	Sito-750-M Yield (%)[a]
1				46	41	61
2				88	87	67
3				30	79	26
4				95	97	80
5				77	76	66
6				32	25	18
7				72	67	61
8				32	16	30

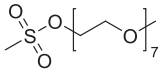
Table 4
Recycling in the ring-closing metathesis reaction under micellar media with designer surfactants **Sito-350-M** and **Sito-750-M**. a) Determined by NMR.

Yield 5 (%)[a] Cycle	1	2	3	4
Sito-750-M	34	33	25	40
TPGS-750-M	93	93	90	99

methanol containing 0.1% trifluoroacetic acid and the solution injected by syringe pump. GC–MS analyses were carried out on a MSD Agilent Technologies EI source, injected by GC System Agilent Technologies equipped with HP-5MS column, with the following temperature programming: 50 °C for 2 min, then ramping 10 °C/min up to 300 °C, then 300 °C for 10 min, solvent delay: 4 min. Reagents and solvents with high purity degree purchased by the providers were used as given. Otherwise, they were purified following the procedures reported in literature. Anhydrous solvents were prepared by adding activated 3 and 4 Å molecular sieves to the solvent under inert atmosphere. Molecular sieves were activated shortly before the use by continuous heating under vacuum. Flash chromatography were done with silica gel Merk 60, 230–400 mesh, following procedures reported in literature [25].

4.2. Experimental procedures

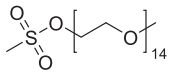
2,5,8,11,14,17,20-heptaoxadocosan-22-yl methanesulfonate (**2a**):



2a

In a 100 mL round-bottomed flask, MPEG 350 (**1a**; 5.0 g, 15 mmol) was heated at 80 °C for 30 min under vacuum, in order to remove traces of moisture. The system was cooled to room temperature under Ar and dry THF (52 mL) and triethyl amine (2.83 g, 3.9 mL, 19 mmol) were added. The mixture was cooled to 0 °C and a solution of methanesulfonyl chloride (7.0 g, 4.7 mL, 61 mmol) in dry THF (10 mL) was added dropwise. The solution was allowed to return to room temperature overnight. The resulting mixture was filtered on a celite plug and the liquors were concentrated in vacuum. The residue was diluted in DCM (300 mL) and saturated aqueous $NaHCO_3$ (300 mL), maintaining the emulsion in vigorous stirring for 40 h. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (3 × 100 mL), dried over $MgSO_4$, filtered and concentrated in vacuum. The product was obtained as a yellow oil (5.49 g, 13 mmol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.27–5.20 (3H, set of m), 4.33–4.22 (2H, set of m), 3.72–3.62 (2H, set of m), 3.59–3.50 (19H, set of m), 3.48–3.41 (2H, set of m), 3.32–3.24 (3H, set of m), 3.05- 2.92 (3H, set of m). ^{13}C{^{1}H} NMR (100 MHz): δ 71.7, 70.4, 70.4, 70.3, 69.3, 68.8, 58.8, 58.8, 53.5, 37.5, 37.5, 31.5, 30.1.

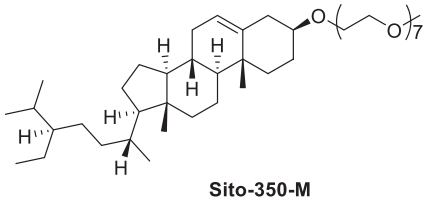
2,5,8,11,14,17,20,23,26,29,32,35,38,41-tetradecaoxatritetracontan-43-yl methanesulfonate (**2b**):



2b

In a 100 mL two-necked round-bottomed flask, MPEG 750 (**1b**; 11.250 g, 17.3 mmol) was heated at 80 °C for 30 min under vacuum, in order to remove traces of moisture. The system was cooled to room temperature under Ar and dry THF (40 mL) and triethyl amine (2.83 g, 3.9 mL, 19 mmol) were added. The mixture was cooled to 0 °C and a solution of methanesulfonyl chloride (7.0 g, 4.7 mL, 61 mmol) in dry THF (5 mL) was added dropwise. The solution was allowed to return to room temperature over two days. The resulting mixture was filtered on a celite plug and the liquors were concentrated in vacuum. The residue was diluted in DCM (300 mL) and saturated aqueous $NaHCO_3$ (300 mL), maintaining the emulsion in vigorous stirring for 40 h. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (3 × 100 mL), dried over $MgSO_4$, filtered and concentrated in vacuum. The product was obtained as a pale waxy solid (8.20 g, 11.3 mmol, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.38–4.36 (m, 2H), 3.77–3.75 (m, 2H), 3.68–3.59 (m, 50H), 3.37 (s, 3H), 3.07 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 72.1, 70.8, 70.71, 70.65, 69.4, 69.2, 59.2, 37.9; LCMS (ESI): calcd. for $C_{31}H_{66}O_{18}S$ $[M+Na]^+$ 758.397; found: 757.399.

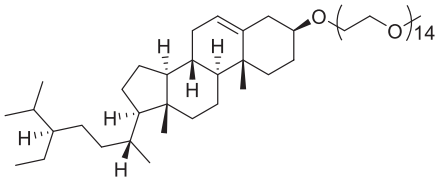
22-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)−17-((2*R*,5*R*)−5-ethyl-6-methyl heptan-2-yl)−10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-3-yl)oxy)−2,5,8,11,14,17,20-heptaoxadocosane (**Sito-350-M**):



Sito-350-M

In a 100 mL three-necked round-bottomed flask equipped with argon inlet and septum, β-sitosterol (161 mg, 0.39 mmol) was dissolved in anhydrous toluene (25 mL) and sodium hydride (320 mg, 7.80 mmol) was added. The mixture was then kept under vigorous stirring for 48 h. A solution of **2a** (127 mg, 0.30 mmol) in anhydrous toluene (7 mL) was then added dropwise. After the addition was complete, the mixture was stirred at 50 °C for 5 days. Afterwards, the reaction was quenched with isopropyl alcohol (10 mL). The solvent was then removed and the solid suspended in dichloromethane. The salts were separated by centrifugation and the clear solution was concentrated with rotavapor. The excess of β-sitosterol was then removed by silica gel filtration eluting with dichloromethane and ethyl acetate (in gradient from 6:4 to pure ethyl acetate) to obtain the product as a yellow oil (77.5 mg, 0.11 mmol, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33–5.28 (m, 1H), 3.82–3.41 (m, 28H, PEG), 3.35 (s, 3H), 3.19–3.10 (m, 1H), 2.36–2.31 (m, 1H), 2.21–2.13 (m, 1H), 2.06–0.45 (m 45H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.03, 121.58, 79.54, 72.00, 70.95, 70.67, 70.64, 70.57, 67.36, 59.08, 56.84, 56.12, 50.25, 45.89, 42.38, 39.84, 39.14, 37.31, 36.93, 36.20, 34.00, 32.01, 31.96, 29.75, 29.21, 28.43, 28.31, 26.14, 24.36, 23.13, 21.13, 19.88, 19.44, 19.11, 18.85, 12.05, 11.92; LCMS (ESI): calcd. for $C_{44}H_{80}NaO_8$ $[M+Na]^+$ 760.106; found: 760.084.

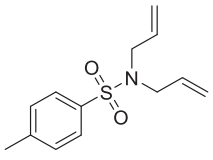
43-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)−17-((2*R*,5*R*)−5-ethyl-6-methyl heptan-2-yl)−10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-3-yl)oxy)−2,5,8,11,14,17,20,23,26,29,32,35,38,41-tetradecaoxatritetracontane (**Sito-750-M**):



Sito-750-M

In a 100 mL three-necked round-bottomed flask equipped with argon inlet and septum, β-sitosterol (805 mg, 1.94 mmol) was dissolved in anhydrous toluene (20 mL) and sodium hydride (930 mg, 38.80 mmol) was added. The mixture was then kept under vigorous stirring overnight. A solution of **2b** (1.26 g, 1.73 mmol) in anhydrous toluene (23 mL) was then added dropwise. After the addition was complete, the mixture was stirred at 50 °C for 3 days, raising the temperature up to 65 °C for another 2 days. Afterwards, the reaction was quenched with isopropyl alcohol (10 mL). The solvent was then removed and the solid suspended in dichloromethane. The salts were separated by centrifugation and the clear solution was concentrated with rotavapor. The excess of β-sitosterol was removed by silica gel filtration eluting with ethyl acetate and the product was recovered pale yellow wax eluting with methanol (1.06 g, 1.01 mmol, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35–5.31 (m, 1H), 3.85–3.43 (m, 56H, PEG), 3.37 (s, 3H), 3.22–3.13 (m, 1H), 2.39–2.33 (m, 1H), 2.24–2.1 (m, 1H), 2.08–0.50 (m 45H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.13, 121.68, 79.64, 72.09, 71.03, 70.75, 70.71, 70.66, 67.43, 59.17, 56.93, 56.22, 50.34, 45.99, 42.48, 39.93, 39.21, 37.39, 37.02, 36.29, 34.10, 32.10, 32.05, 29.31, 28.51, 28.39, 26.24, 24.44, 23.22, 22.21, 21.21, 19.96, 19.53, 19.18, 18.93, 12.13, 12.00; LCMS (ESI): calcd. for $C_{58}H_{108}NaO_{15}$ $[M+Na]^+$ 1068.477; found: 1067.828.

N,*N*-diallyl-4-methylbenzenesulfonamide (**4**):



4

In a 100 mL round-bottomed flask, to a solution of 4-methylbenzenesulfonamide (684.9 mg, 4 mmol) in acetonitrile (40 mL), allyl bromide (0.87 mL, 10 mmol) and K_2CO_3 (10 mmol,

1.38 g) were added. The mixture was refluxed for 23 h (110 °C, 1000 rpm). Afterwards, the solvent was removed with rotavapor. The solid residue was dissolved in dichloromethane (30 mL) and the mixture was washed with water (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in *vacuum*. The product was obtained as a yellow oil (804.3 mg, 3.2 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 2H, J = 8.3 Hz), 7.30 (d, 2H, J = 8.1 Hz), 5.67–5.56(m, 2H), 5.17–5.11 (m, 4H), 3.80 (d, 4H, J = 6.3 Hz), 2.43 (s, 3H).

Suzuki-Miyaura cross-coupling reaction general procedure for catalytic activity tests:

The surfactant solutions (1.0 mL, a: 1% wt. solution of **Triton X-100** in water; b: 2% wt. solution of **TPGS-750-M** in water; c: 1% wt. solution of **Sito-350-M** in water; d: 2% wt. solution of **Sito-750-M** in water) were added to $PdCl_2(PPh_3)_2$ (2.5 mg, 0.0036 mmol, 0.5 mol%) respectively into four 4 mL vials equipped with a 12 × 4 mm magnetic stirring bar stirred at 500 rpm for a few minutes. Boronic acid (0.72 mmol), aryl bromide (0.72 mmol) and triethylamine (100 μL, 0.72 mmol) were added in sequence and the resulting suspensions were stirred at 1000 rpm for 6 h at room temperature. The mixtures were extracted with AcOEt (2 mL), volatile materials were removed at reduced pressure and the residues were dissolved in $CDCl_3$ and submitted to ^{1}H NMR analyses. ^{19}F NMR spectra were recorded if fluorinated reagents were employed.

Ring-closing metathesis reaction general procedure for recyclability tests:

The surfactant solutions (1.0 mL, a: 2% wt. solution of **TPGS-750-M** in water; b: 2% wt. solution of **Sito-750-M** in water) were added to Grubbs-II catalyst (1.7 mg, 0.002 mmol, 2 mol%) respectively into two 4 mL vials equipped with a 12 × 4 mm magnetic stirring bar stirred at 500 rpm for a few minutes. *N,N*-diallyl-4-methylbenzenesulfonamide **4** (23 μL, 0.10 mmol) was added and the mixtures were stirred at 1000 rpm for 18 h at room temperature. The mixtures were extracted with Et_2O (2 mL), volatile materials were removed at reduced pressure and the residues were dissolved in $CDCl_3$ and submitted to ^{1}H NMR analyses. After recovery of the aqueous phase, fresh Grubbs-II catalyst (1.7 mg, 0.002 mmol) and amide **4** (23 μL, 0.10 mmol) were added. The reaction was then performed similarly as above. The reaction cycle was repeated for three times.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2022.122316.

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