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"TPG-lite": A new, simplified "designer" surfactant for general use in synthesis under micellar catalysis conditions in recyclable water

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ABSTRACT

Using the oxidized, carboxylic acid-containing form of MPEG-750, esterification with racemic vitamin E affords a new surfactant (TPG-lite) that functions as an enabling, nanoreactor-forming amphiphile for use in many types of important reactions in synthesis. The presence of a single ester bond is suggestive of simplified treatment as a component of (eventual) reaction waste water, after recycling. Many types of reactions, including aminations, Suzuki-Miyaura, S_NAr, and several others are compared directly with TPGS-750-M, leading to the conclusion that TPG-lite can function as an equivalent nanomicelle-forming surfactant in water. Prima facie evidence amassed via DLS and cryo-TEM analyses support these experimental observations. In silico evaluations of the aquatic toxicity and carcinogenicity of TPG-lite indicate that it is safe to use.

1. Introduction

As the world attempts to simultaneously better understand and deal with environmental issues that are wreaking havoc throughout modern day society, the buildup of organic waste created by the chemistry enterprise is certainly not helping the situation, as it continues unabated. Since most (e.g., >80%, as used by the pharmaceutical industry) can be attributed directly to organic solvents in which reactions in all areas of chemistry are typically run, global petroleum resources are constantly being depleted. Clearly, such supplies are limited, making the manner in which modern organic synthesis is practiced clearly unsustainable. For several years, our thesis in this regard has been very simple: chemo-catalysis must follow Nature's lead [1] and be converted, as with bio-catalysis, to a predominantly, if not exclusively, water-based discipline [2].

The overarching approach enabling this switch has focused on many of the features associated with enzymatic catalysis as the model: build enzyme-like hydrophobic pockets using newly engineered surfactants that form nanoparticles in water [3]. These nanomicelles accommodate water-insoluble educts and catalysts and hence, in essence, function as "non-lock and key" enzymes; i.e., they operate in water without limitations imposed by such bio-catalysis phenomena, yet function similarly as nanoreactors [4].

Several designer surfactants [5] have been described previously by us and others, with each serving a particular synthetic need. Thus, while PTS [5a] (**1**; Fig. 1) was initially employed to test the ability of such amphiphiles to enable various reactions of importance in synthesis, it was the next generation surfactant, TPGS-750-M [5b] (**2**) that has remained the workhorse, micelle-forming material shown to be of broad synthetic utility. Its unique organization of smaller (ca. 10 nm) nanomicelles in close proximity, occupying the interior of larger (45–60 nm) nanoparticles may account for its general utility [4]. It was selected to include a succinic acid linker, rather than one based on sabacic acid as in PTS, since opening succinic anhydride by α-tocopherol guaranteed a single ester as product in high yield, while the analogous reaction with sebacoyl dichloride affords mixtures of mono- and diester products, Nonetheless, other factors have arisen over time that point to potential limitations associated with TPGS-750-M, thereby encouraging us to design new surfactants that solve specific synthetic needs. Thus, Nok [5c] (**3**) was developed as an alternative to **2**, given that

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0040-4020/

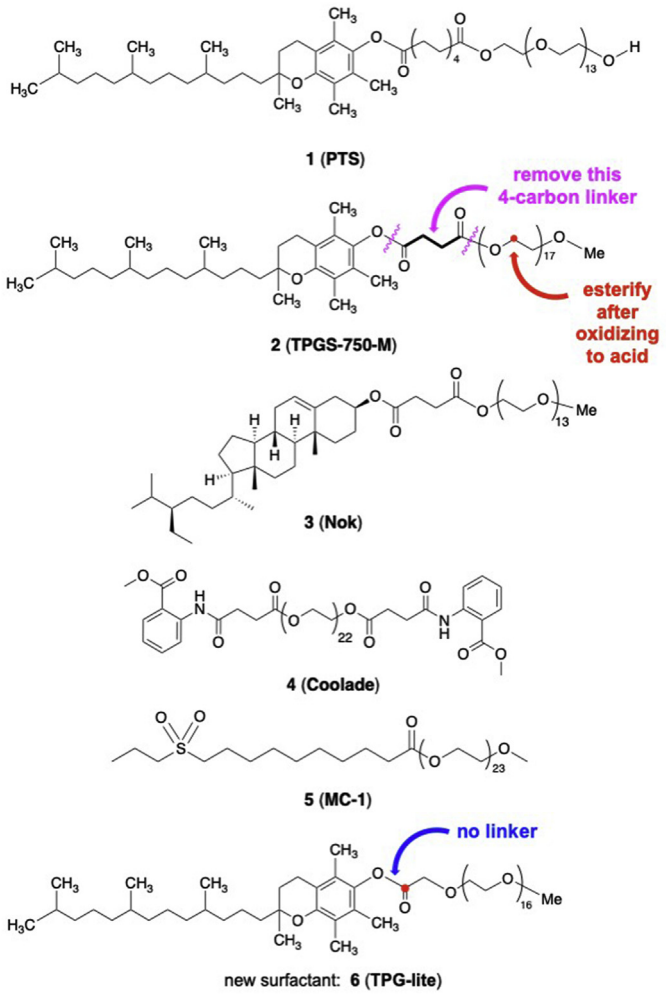


Fig. 1. Designer surfactants for use in numerous reactions under aqueous micellar conditions.

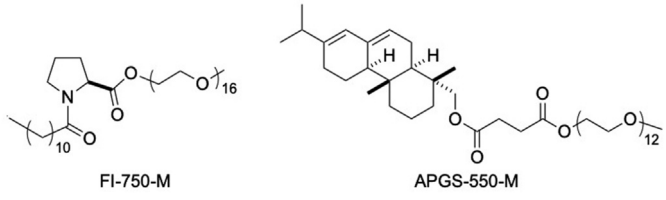


Fig. 2. Structure for TPG-lite (i.e., TPGS-750-M without the succinic acid linker).

commodity chemicals such as vitamin E can be, at times, in short supply. Coolade [5d] (**4**) was fashioned as a non-foaming surfactant, and hence, especially useful for synthetic situations involving gases, whether needed throughout or generated during a reaction; it does not foam. Lastly, MC-1 [5e] (**5**) was introduced as a seemingly ideal amphiphile for peptide bond constructions in aqueous micellar media, as it contains within its inner (and typically non-polar) core a polar sulfone residue, mimicking a traditional polar peptide medium, such as DMSO. Other significant and recent contributions along these lines include proline-derived Fl-750-M from Handa and co-workers [6], and terpene-containing APGS-550-M from the Huang group [7] (see Fig. 2).

As generally useful TPGS-750-M has been since its introduction in 2011 [5b], there remains several features associated with its preparation, use, and ***removal from (relatively modest) waste water streams.*** In this report, we describe a new, simpler version of **2** called "TPG-lite" (**6**), streamlining its synthesis, outlining its general applicability, and by virtue of its sole ester linkage, ***minimizing the chemistry likely required for downstream processing looking towards its decomposition***.

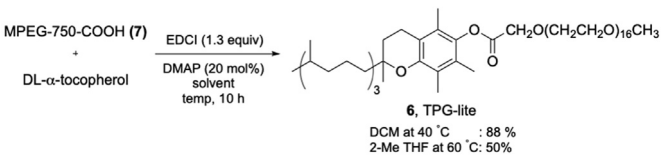
2. Results and discussion

2.1. Preparation of TPG-lite

The design of TPS-lite was contemplated on eliminating the 4-carbon, succinic acid linker, which we speculated was not key to the imparted features characteristic of these nanoparticles. By using the carboxylic form of the mono-primary alcohol in MPEG-750 (**7**), esterification with racemic α-tocopherol directly afforded TPG-lite (Scheme 1). This *waxy, light yellow-colored material* is shown in Fig. 3. Several of the properties of **6** were tested, including its acidity when dissolved in water at the 2 wt % (i.e., 20 mg in 1 mL of water), which is pH = 7. By contrast, TPGS-750-M at the same concentration in water typically and reproducibly shows a pH = 4, perhaps reflecting retention of acid within its PEG region (if purified via column chromatography, the acidic impurities are removed and the pH increases to 6.8). The stability of monoester **6** was tested under usual Suzuki-Miyaura reaction conditions (Scheme 2). The results indicate that, as with precursor surfactant **2**, the presence of the two methyl residues at the two *ortho*-positions in vitamin E-based ester **6** afford considerable stability to this micelle-forming surfactant at 45 °C. Nonetheless, **6** does undergo hydrolysis to give the expected two products from which it was formed at 75 °C. On the other hand, this stability suggests that its decomposition when part of a waste water stream that eventually forms will require somewhat more forcing conditions, akin to those described by Novartis in their treatment of **2** [8]. Of course, the absence of the MPEG ester automatically eliminates one of the hydrolysis steps required in the processing of TPGS-750-M.

2.2. In silico analyses of toxicity

The structure of TPG-lite (**6**) was assessed using previously developed design guidelines for minimal aquatic toxicity [9] and the CADRE-AT model [10]. Design guidelines for minimal ecotoxicity define a 'safer' chemical space based on cutoffs in key physicochemical properties that affect bioavailability, namely octanol-water distribution coefficient at physiological pH (log $D_{7.4}$) and reactivity, which is broadly characterized using the HOMO-LUMO gap. From Fig. 4, TPG-lite and TPGS-750-M have nearly identical band gap values (6.15 and 6.04 eV, respectively) as well as log D values (10.3 and 9.6, respectively), owing to similar structure. While neither falls within the 'safer chemical space', i.e. left upper quadrant in Fig. 4, it is important to recognize that the design guidelines for minimal ecotoxicity do not assert that compounds outside this quadrant are unsafe; they merely affirm that compounds within these property cutoffs are statistically more likely to be safe [9]. Like Vitamin E, TPG-based surfactants have high log D values, indicating



Scheme 1. Preparation of **6**, TPG-lite.

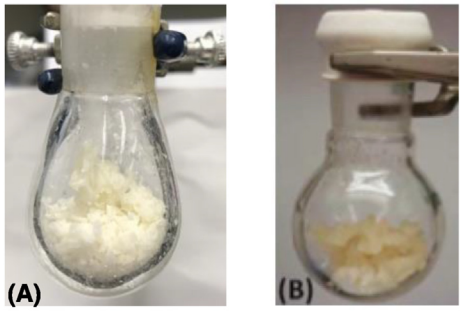
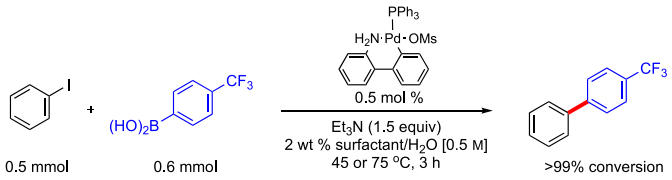


Fig. 3. Neat surfactants: (**A**) TPG-lite; (**B**) TPGS-750-M.



surfactant	temperature (°C)	recovery of surfactant (%)*
TPGS-750-M (**2**)	45	91
TPG-lite (**6**)	45	90
TPGS-750-M (**2**)	75	60
TPG-lite (**6**)	75	82

*Surfactant recovered after Suzuki-Miyaura coupling

Scheme 2. Surfactant stability in SM couplings.

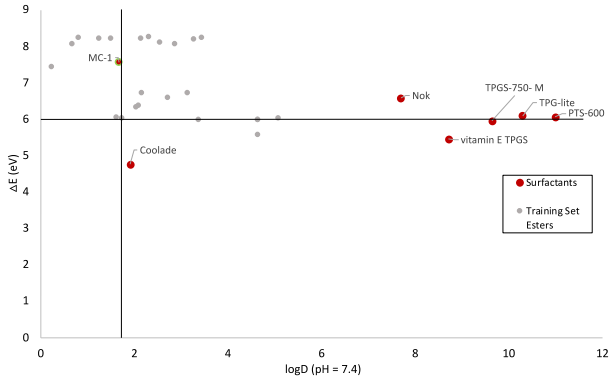


Fig. 4. *In silico* analysis of aquatic toxicity. Application of design guidelines for minimal ecotoxicity to a series of surfactants. 'Safer' chemical space in the upper left quadrant is marked by cutoffs in log $D_{7.4}$ (1.7) and D*E* (6 eV). Grey dots represent esters in the model training set with 'similar' structures to TPG-containing surfactants used in this study.

these compounds are readily bioavailable, which is hardly surprising but does not mean, *a priori,* that they are hazardous. Band gap values, which indicate broader acid-base reactivity with biological targets, are lower (i.e. implying greater reactivity) for TPG compounds than for Nok or MC-1, owing to ester groups proximal to an aromatic ring. TPG-lite is slightly less reactive than TPGS-750-M, consistent with greater electron delocalization in the ester group.

Because the application of design guidelines for minimal ecotoxicity was somewhat inconclusive, we screened both TPG-lite and TPGS-750-M using the CADRE-AT model [10]. CADRE-AT relies on molecular simulations and density functional theory (DFT) to compute a host of mechanistically-relevant physico-chemical properties and electronic parameters in order to predict an LC_{50} value in a statistical model. CADRE-AT has been externally validated and shown to outperform other existing *in silico* tools used for this endpoint [10]. In our analysis, predicted thresholds for both TPG-lite and TPGS-750-M were LC_{50} = 755 mg/L and LC_{50} = 462 mg/L, corresponding to CADRE-AT categories of concern of low and none, respectively. According to the US EPA's Safer Choice guidelines, both compounds can be categorized as 'practically non-toxic' based on predicted LC_{50} values. Thus, our results indicate these chemicals are not hazardous to aquatic species, with TPG-lite likely being an even safer alternative to TPGS-750-M.

2.3. Toxicology & biodegradability

Compared to the now well-described and understood TPGS-750-M, TPGS-lite is devoid of its linker while containing the same vitamin E and PEG-750-M moieties. As such, it retains the same toxicological properties that makes it benign. No structural concern for mutagenicity was detected (i.e., no unclassified or misclassified features, based on Derek and Sarah Nexus and Case Ultra models) [11].

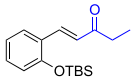
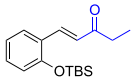
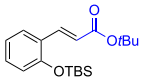
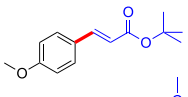
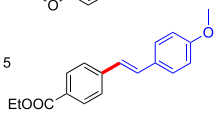
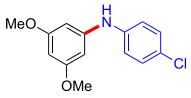
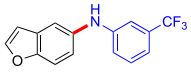
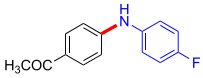
From a biodegradability standpoint, while simpler chemically, this novel surfactant suffers from a point of entry for biodegradation. With the succinic acid used as a linker, TPGS-750-M and other related surfactants start being degraded at the least sterically accessible ester, which leads to digestion more readily for PEG-750-M, thus making TPGS-750-M a biodegradable, non-accumulative species [8]. By contrast, this two-component novel surfactant lacks this soft spot in its structure. TPGS-lite, therefore, is expected to be somewhat less biodegradable than is TPGS-750-M, although the extent of the impact remains to be confirmed by experimental data.

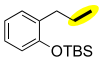
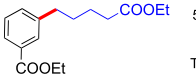
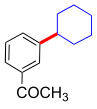
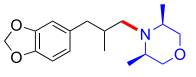
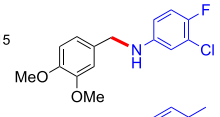
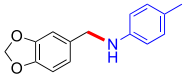
2.4. Comparisons between TPG-lite and TPGS-750-M

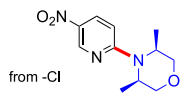
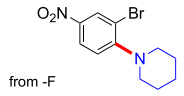
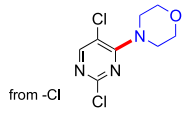
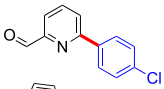
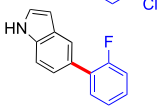
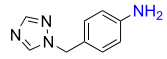
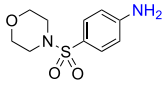
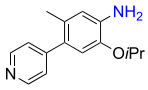
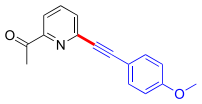
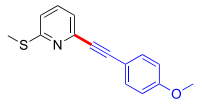
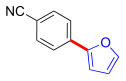
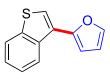
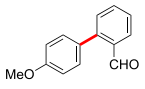
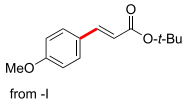
As noted above, the relative stability of TPGS-750-M (**2**) *vs.* that of TPG-lite (**6**) was tested using a Suzuki-Miyaura coupling at various temperatures, after which the surfactants were recovered by column chromatography and their integrity analyzed by ^{1}H NMR. As shown in Scheme 2, the monoester in **6** protected by the 2,6-dimethyl groups present in α-tocopherol leads to a more stable surfactant, whereas the more accessible MPEG ester in **2** leads to its more rapid hydrolysis at 75 °C.

All of these indicators, however, do not guarantee that TPG-lite will serve as an enabling technology for the many varied applications for which TPGS-750-M is now known to mediate in water [12]. Hence, an extensive evaluation was undertaken to determine if **6** offers the same broad-based opportunities, potentially functioning either as an equivalent, or even a replacement, for surfactant **2**. Table 1 outlines several reaction types involving common transition metal-catalyzed reactions in TPGS-750-M [13] up against TPG-lite. With our recent attention to the "endangered" status of palladium, meaning that access to this precious metal is limited by the mining technology available in addition to the potential for geopolitical issues to come into play, several of our newly developed procedures using Pd at the ppm level of catalysis [14] (e.g., hydrogenation, reductive amination, nitro group reduction, and aminations) were also screened in these studies. Another important, albeit non-transition metal-based reaction, S_NAr [13f] processes, was included in these comparisons. What was observed is that in all cases, these surfactants are virtually interchangeable, including the rates of reactions. Additional studies wherein TPG-lite-derived nanomicelles enabled various reactions in water can

Table 1
Comparisons between TPGS-750-M and TPG-lite

Entry	Compound	Conditions	Yield (TPG-lite)	Yield (TPGS-750-M)
		cross metathesis		
1		alkene (3.0 equiv) Grubbs-G2 (2 mol %) rt, 4.0 h	53%	49%
2		alkene (3.0 equiv) Grubbs-G2 (2 mol %) 0.02 M $KHSO_4$, rt, 4.0 h	90%	88%
3		alkene (3.0 equiv) Grubbs-G2 (2 mol %) rt, 12.0 h	90%	83%
		Heck couplings		
4		2 mol% $[P(t\text{-}Bu_3)]_2Pd$ alkene (2.0 equiv) $K_3PO_4{\cdot}H_2O$ (3.0 equiv) NaCl (3 M) 45 °C, 5 h	95%	95%
5		2 mol% $[P(t\text{-}Bu_3)]_2Pd$ styrene (2.0 equiv) $K_3PO_4{\cdot}H_2O$ (3.0 equiv) NaCl (3 M), 45 °C, 5 h	93%	90%
		amination		
6		[*t*-BuXPhosPd(cinnamyl)]OTf (1000 ppm), amine (1.2 equiv), KO-*t*-Bu (1.5 equiv) 10% THF, 45 °C, 16 h	93%	90%
7		[*t*-BuXPhosPd(cinnamyl)]OTf (1000 ppm), amine (1.2 equiv), KO-*t*-Bu (1.5 equiv) 10% THF, 45 °C, 16 h	91%	92%
8		[*t*-BuXPhosPd(cinnamyl)]OTf (1000 ppm), amine (1.2 equiv), KO-*t*-Bu (1.5 equiv) 10% THF, 45 °C, 16 h	97%	97%

Entry	Compound	Conditions	Yield (TPG-lite)	Yield (TPGS-750-M)
		hydrogenation		
9		500 ppm 1 wt % Pd/C H_2 balloon, rt, 2.0 h	quant	quant
10		500 ppm 1 wt % Pd/C H_2 balloon, rt, 10.0 h	quant	quant
11		500 ppm 1 wt % Pd/C H_2 balloon, rt, 2.0 h	quant	quant
		Negishi couplings		
12		5000 ppm $(Amphos)_2PdCl_2$ alkyl bromide (3.0 equiv) Zn powder (4.0 equiv) TMEDA (1.0 equiv), rt, 24 h	78%	75%
13		5000 ppm $(Amphos)_2PdCl_2$ alkyl bromide (3.0 equiv) Zn powder (4.0 equiv) TMEDA (1.0 equiv), rt, 24 h	73%	71%
		reductive amination		
14		2000 ppm 1 wt % Pd/C 1.5 equiv Et_3SiH, 45 °C 4.0 h	93%	92%
15		2000 ppm 1 wt % Pd/C 1.1 equiv Et_3SiH, 45 °C 4.0 h	78%	75%
16		2000 ppm 1 wt % Pd/C 1.1 equiv Et_3SiH, 45 °C 3.0 h	97%	95%

Entry	Compound	Conditions	Yield (TPG-lite)	Yield (TPGS-750-M)
		S_NAr reactions		
17		amine (1.1 equiv) $K_3PO_4{\cdot}H_2O$ (1.2 equiv) 45 °C, 2.0 h	99%	90%
18		amine (1.1 equiv) $K_3PO_4{\cdot}H_2O$ (1.2 equiv) 45 °C, 2.0 h	99%	98%
19		amine (1.1 equiv) $K_3PO_4{\cdot}H_2O$ (1.2 equiv) 45 °C, 3.0 h	97%	95%
		Suzuki-Miyaura couplings		
20		300 ppm Handaphos pre-cat boronic acid (1.2 equiv) Et_3N (2.0 equiv) 45 °C, 16 h	97%	95%
21		300 ppm Handaphos precat boronic acid (1.2 equiv) Et_3N (2.0 equiv) 10% THF, 45 °C, 20 h	95%	92%
		nitro group reductions		
22		4000 ppm Pd/C H_2 45 °C, 10 h	95%	96%
23		4000 ppm Pd/C H_2 45 °C, 10 h	95%	97%
24		4000 ppm Pd/C H_2 45 °C, 10 h	93%	93%
		Sonogashira couplings		
25.		500 ppm $[(cinnamyl)PdCl]_2$ 3000 ppm cBRIDP alkyne (1.2 equiv) $K_3PO_4{\cdot}H_2O$ (2.0 equiv) 45 °C, 4 h	92	90
26.		500 ppm $[(cinnamyl)PdCl]_2$ 3000 ppm cBRIDP alkyne (1.2 equiv) $K_3PO_4{\cdot}H_2O$ (2.0 equiv) 45 °C, 6 h	93	95
		Stille couplings		
27.		2 mol% $Pd[P(t\text{-}Bu_3)]_2$ Ar-$SnBu_3$ (1.2 equiv) DABCO (3.0 equiv) NaCl (1.0 equiv) rt, 5 h	80	81
28.		2 mol% $Pd[P(t\text{-}Bu_3)]_2$ Ar-$SnBu_3$ (1.2 equiv) DABCO (3.0 equiv) NaCl (1.0 equiv) rt, 3 h	81	83
		Fe/ppm Pd NPs catalyzed Suzuki-Miyuara coupling		
29.		350 ppm Pd boronic acid (1.2 equiv) $K_3PO_4{\cdot}H_2O$ (1.5 equiv) 45 °C, 24 h	95	92
		Fe/ppm Pd NPs catalyzed the Heck coupling		
30.		1000 ppm Pd alkene (2.0 equiv) NaCl (6.0 equiv) $K_3PO_4{\cdot}H_2O$ (3.0 equiv) rt, 24 h	91	90

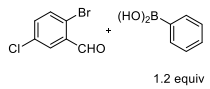
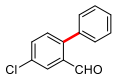
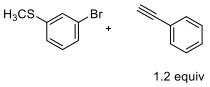
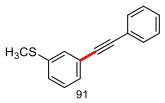
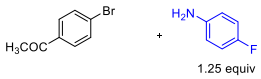
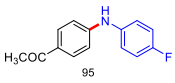
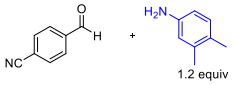
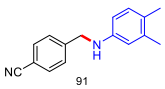
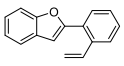
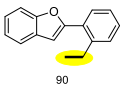
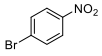
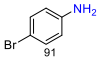
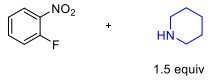
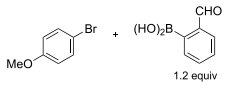
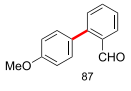
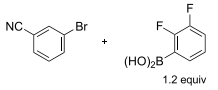
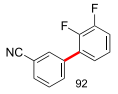
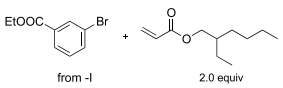
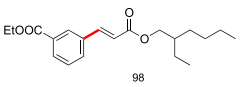
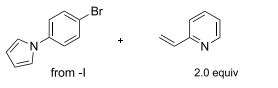
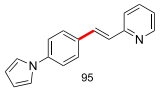
[a]Isolated yields

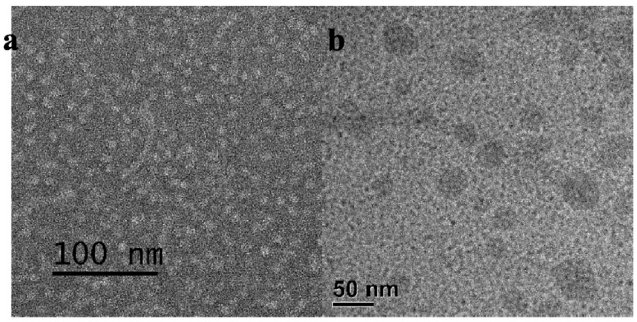
be found in Table 2. As shown, couplings that include entries 1–4 were all successful, at least suggestive that, again, micelles derived from **6** function efficiently as nanoreactors in water.

2.5. Analyses of TPG-lite by cryo-TEM and DLS

As with prior analyses of surfactants **1**–**5**, both dynamic light scattering (DLS) and cryo-TEM experiments were conducted to establish similarities and/or differences in aggregation state, as well as individual particle shape and size of the nanoreactors in which the chemistry is presumably happening. As shown in Fig. 5, DLS measurements indicated that the particle size was very much within the same 45–60 nm range previously observed for TPGS-750-M. Most revealing, however, were the cryo-TEM data, that indicated the presence of several types of nanoparticles. Thus, as seen in Fig. 5, image c, aqueous solutions of TPG-lite contain several individual smaller spheres of ca. 15 nm, along with longer worm-like arrays as seem previously within PTS [5a] and Nok [5c] and larger, spherical particles averaging ca. 60 nm. This combination of varying sizes and shapes appears to be unique in terms of surfactants applied to organic synthesis seen to date. But as the broad curve associated with the DLS data indicates (images a and b), the overall average size is very close to that of TPGS-750-M, perhaps explaining the similarity of results found, seemingly independent of reaction type.

Table 2
Additional examples using aqueous TPG-lite.

entry	reactants	conditions	products isolated yield (%)
1.	**S-M coupling**  1.2 equiv	300 ppm precat **A** Et_3N 1.0 equiv 2 wt % TPG-lite/H_2O [0.5 M] 45 °C, 24 h	 90
2.	**Sonogashira coupling**  1.2 equiv	750 ppm [(cinnamyl)PdCl]$_2$ 4500 ppm cBRIDP K_3PO_4 H_2O (2.0 equiv) 2 wt % TPG-lite/H_2O [0.5 M] 45 °C, 6 h	 91
3.	**Amination**  1.25 equiv	1000 ppm [*t*-BuXphosPd(cinnamyl)]OTf KO-*t*-Bu (1.5 equiv) 2 wt % TPG-lite/H_2O [0.5 M] 45 °C, 1 h	 95
4.	**Reductive amination**  1.2 equiv	2000 ppm Pd/C 1.5 equiv Et_3SiH 2 wt % TPG-lite/H_2O [0.5 M] 45 °C, 6 h	 91
5.	**Hydrogenation** 	500 ppm Pd/C H_2 balloon (1 atm) 2 wt % TPG-lite/H_2O [0.5 M] rt, 10 h	 90
6.	**Nitro reduction** 	CIP (5.0 equiv), NH_4Cl (3.0 equiv) 2 wt % TPG-lite/H_2O [0.5 M] 10% THF, 45 °C, 2 h	 91
7.	**SNAr**  1.5 equiv	K_3PO_4 H_2O (1.0 equiv) 2 wt % TPG-lite/H_2O [0.5 M] 45 °C, 4 h	 93
8.	**Fe/ppm Pd NPs catalyzed S-M couplings**		
	 1.2 equiv	350 ppm Pd K_3PO_4 H_2O (1,5 equiv) 2 wt % TPG-lite/H_2O [0.5 M], 45 °C, 24 h	 87
	 1.2 equiv	350 ppm Pd K_3PO_4 H_2O (1,5 equiv) 2 wt % TPG-lite/H_2O [0.5 M], 45 °C, 24 h	 92
9.	**Fe/ppm Pd NPs catalyzed the Heck couplings**		
	 from -I 2.0 equiv	2500 ppm Pd NaCl (6,0 equiv) K_3PO_4 H_2O (3,0 equiv) 2 wt % TPG-lite/H_2O [0.5 M], rt, 24 h	 98
	 from -I 2.0 equiv	2500 ppm Pd NaCl (6,0 equiv) K_3PO_4 H_2O (3,0 equiv) 2 wt % TPG-lite/H_2O [0.5 M], rt, 24 h	 95



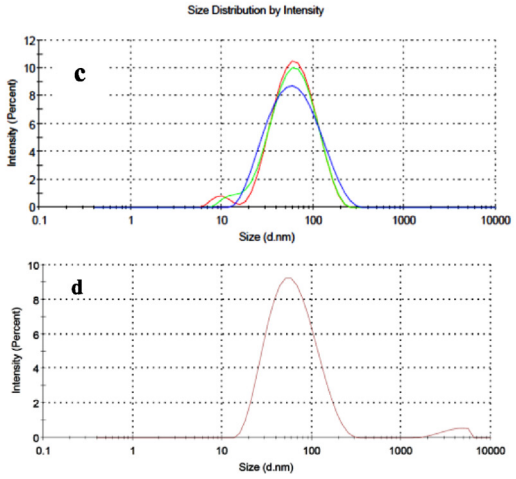
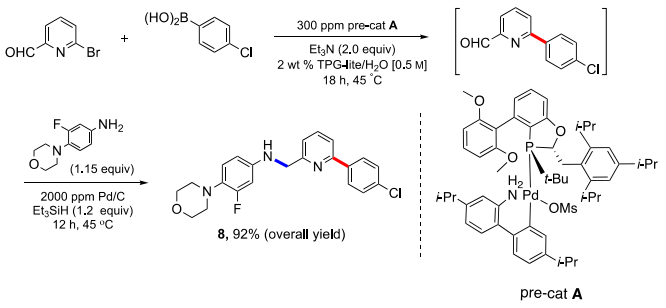


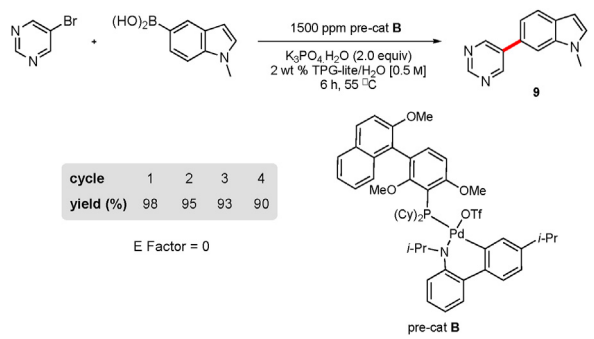
Fig. 5. cryo-TEM data: image **a** for **6**, image **b** for **2**; and DLS: image **c** for **6**, image **d** for **2**.

2.6. Tandem sequences in TPG-lite

Since the disclosure of TPGS-750-M almost a decade ago, we have endeavored to illustrate the potential for multiple reaction sequences to be carried out in 1-pot operations, further minimizing waste and saving considerable time by no longer requiring a workup with each successive step. Scheme 3 illustrates that TPG-lite is also prone to enabling such telescoping of reaction sequences, as shown in Scheme 3.



Scheme 3. 1-Pot tandem sequence.



Scheme 4. Recycling of aqueous TPG-lite and E Factor.

2.7. Recycling and E factor determination

The potential for recycling of these aqueous reaction mixtures containing surfactant **6** is illustrated in Scheme 4. Here, the solid product **9** could be isolated simply via filtration, while the aqueous reaction mixture, as usual, is readily recycled, thereby minimizing waste water streams. The associated E Factor for this reaction in TPG-lite, based on organic solvent usage was, therefore zero.

3. Conclusions

TPG-lite has been developed to function akin to established TPGS-750-M as an enabling, nanomicelle-forming surfactant. Unlike its precursor, this amphiphile is devoid of a linker between it lipophilic (vitamin E) portion and its hydrophilic (MPEG-750) section, thereby containing only a single ester linkage potentially improving its economic footprint, and its stability due to the highly hindered ester. It can be used interchangeably in all representative reactions studied to date that feature direct comparisons, including those involving ppm level Pd catalysis. Based on *in silico* evaluations, TPG-lite appears, not unexpectedly given its otherwise close relationship to TPGS-750-M, to be safe towards both human and aquatic life. Its presence in water gives rise to nanomicelles that are closely related to those of its precursor, as seen via both DLS and cryo-TEM measurements. Recycling of such aqueous reaction mixtures containing TPG-lite is straightforward, while its use in a representative coupling indicates that low E Factors, attesting to its extent of "greenness", are to be expected. Additional, newly designed, and unprecedented alternative surfactants to those in this series are under development and will be disclosed in future reports from these labs.

4. Experimental section

Reagents and chemicals were purchased from Sigma-Aldrich, Combi-Blocks, Alfa Aeser, or Acros Organics and used without further purification. Solvents were obtained from an Innovative Technologies Solvent Purification System (SPS) and used immediately. Deuterated solvents were purchased from Cambridge Isotopes Laboratories. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 500 MHz (500 MHz for ^{1}H, 125 MHz for ^{13}C); DMSO-d_6, CD_3OD, and $CDCl_3$ were used as NMR solvents. The chemical shifts are reported in parts per million (ppm), the coupling constant J values are given in Hertz (Hz). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. High-resolution mass analyses were obtained using a 5975C Mass Selective S-3 Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). As capillary column, a HP-5MS cross linked 5% phenylmethylpolysiloxanediphenyl column (30 m × 0.250 mm, 0.25 μm, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min. Thin layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). Flash chromatography was performed in glass columns using Silica Gel 60 (EMD, 40–63 μm) and using Biotage Isolera instruments. GC-MS data were recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). TPGS-750-M was either prepared or supplied by PHT international (also available from Sigma-Aldrich, catalog #733857), and 1 wt % Pd/C was purchased from Sigma-Aldrich (#205672). The desired 2 wt % of surfactant solution in HPLC water (which was degassed with argon prior to use) was prepared by dissolving 2 g of surfactant together with 98 g of HPLC water and stored under argon.

4.1. Preparation of TPG-lite

A 100 mL round-bottom flask with magnetic stir bar and septum was charged with MPEG-750-COOH **7**, (8.43 g, 11.00 mmol), DL-α-tocopherol (4.9 g, 11.6 mmol), N-Ethyl-N′-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI) (2.8 g, 14.4 mmol), N,N-Dimethylpyridin-4-amine (DMAP) (270 mg, 20 mol%) and solvent (70 mL DCM or 100 mL 2-Me THF). A rubber septum was put on, and the reaction flask was placed in a pre-heat oil bath (45 or 65 °C) until the reaction reached completion (followed by TLC). The resulting solution was allowed to attain rt, at which point ~55–60 mL of the solvent was recovered via rotary evaporation. The concentrate in *vacuo* was purified by flash column chromatography on silica gel eluting with a 100% DCM to 7% MeOH/DCM gradient to afford TPG-lite **6** (11.7 g, 88%) as very light yellowish white wax. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.46 (s, 2H), 4.19 (s, 2H), 4.01–3.44 (m, 51H), 3.38 (s, 3H), 2.58 (t, J = 6.8 Hz, 2H), 2.08 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H), 1.69 (dt, J = 13.4, 4.1 Hz, 2H), 1.62–1.49 (m, 4H), 1.41–1.33 (m, 4H), 1.24 (d, J = 9.6 Hz, 8H), 1.17–1.03 (m, 8H), 0.96–0.78 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 71.9, 71.0, 70.6, 70.6, 70.6, 68.4, 59.0, 49.0, 39.4, 37.4, 37.4, 34.0, 32.8, 32.7, 28.0, 25.6, 25.0, 24.8, 24.4, 22.7, 22.6, 21.0, 20.6, 19.8, 19.7, 13.0, 12.2, 11.8.

4.2. Experimental procedure for stability studies of TPGS-750-M and TPG-lite in Suzuki-Miyaura coupling

Into a 1-dram screw cap vial containing a PTFE coated magnetic stir bar was added 0.5 mol% of PPh_3-Pd-G3 (with respect to iodobenzene), 0.6 mmol of 4-trifluoromethyl phenylboronic acid. The vial was evacuated and backfilled with argon (this procedure was repeated three times). Iodobenzene (0.5 mmol), triethylamine (0.75 mmol), A 0.5 mL 2 wt % surfactant/H_2O solution were added under argon. The vial was quickly replaced with the screw cap and stirred at 45 °C for 3 h (GC-MS shows complete conversion). The

reaction mixture was adsorbed on silica and purified using flash column chromatography (7% MeOH/DCM) to recover the surfactant.

4.3. General procedure for cross-metathesis (Table 1, entries 1–3)

Into a 1-dram reaction vial containing a PTFE coated magnetic stir bar was added Grubbs second-generation catalyst (4.2 mg, 2 mol %, with respect to alkene) under argon atmosphere. The alkene (0.25 mmol) and acrylate (0.5 mmol) were added sequentially into the vial, and then 0.5 mL 2 wt % surfactant/H_2O solution was added via syringe. The reaction was allowed to stir vigorously for a given time at room temperature. The reaction mixture was then extracted with EtOAc (0.2 mL x 4). The crude product was purified by flash chroma-tography on silica gel.

4.4. General procedure for Heck couplings (Table 1, entries 4–5)

Into a 1-dram reaction vial containing a magnetic stir bar and Teflon-lined septum was added Pd(*t*-$Bu_3P)_2$ (2.6 mg, 2 mol %, with respect to aryl halide) and an aryl halide (0.25 mmol, if solid) inside a glove box. The reaction vial was evacuated and refilled with argon (repeated 3 times). An acrylate/styrene (0.5 mmol), Et_3N (104 μL, 0.75 mmol) and 0.5 mL 2 wt % surfactant/H_2O solution were added under a positive flow of argon. The reaction mixture was stirred vigorously at 45 °C for 5 h, and then reaction was extracted with EtOAc (0.2 mL x 4). The crude product was purified by flash chromatography on silica gel.

4.5. General procedure for Buchwald-Hartwig aminations (Table 1, entries 6–8; Table 2, entry 3)

To a 1-dram reaction vial containing a PTFE coated magnetic stir bar, was added 1000 ppm (0.2 mg) [*t*-BuXPhosPd-(cinnamyl)]OTf pre-catalyst (with respect to aryl halide) and *t*-BuOK (0.375 mmol). The reaction vial was evacuated and refilled with argon (repeated 3 times). A 0.5 mL 2 wt % surfactant/H_2O solution was added to the reaction mixture, which was then briefly stirred for 1 min at 45 °C. Then, aryl halide (0.25 mmol, if liquid) and amine (0.3 mmol) were added via syringe under Ar. The reaction mixture was then stirred vigorously at 45 °C for a given time. The reaction mixture was extracted with EtOAc (0.2 mL x 4). The crude product was purified by flash chromatography on silica gel.

4.6. General procedure for hydrogenation reaction (Table 1, entries 9–11; Table 2, entry 5)

In a 1-dram screw cap open top vial containing a PTFE coated magnetic stir bar, 1.3 mg 1 wt % Pd/C (500 ppm Pd, with respect to alkene), alkene (0.25 mmol) and 0.5 mL 2 wt % surfactant/H_2O solution were added. The reaction vial was closed and a TFE lined silicone SURE-LINK septa was punctured with needle (18 G) attached with pre-filled balloon of hydrogen gas. The headspace of the vial was replaced with H_2 by unscrewing the cap under a positive H_2 flow for ca. 5 sec. Finally, the reaction mixture was stirred at rt for 2–10 h. The reaction mass was either filtered through short plug of silica and washed with EtOAc. Removal of organic solvent led to spectro-scopically pure reduced product.

4.7. General procedure for Negishi couplings (Table 1, entries 12–13)

In a 1-dram reaction vial containing a PTFE coated magnetic stir bar, under an argon containing zinc powder (65.4 mg, 1 mmol) and $PdCl_2(Amphos)_2$ (0.88 mg, 0.5 mol %, with respect to aryl bromide) was added 0.5 mL 2 wt % of surfactant/H_2O solution. *N*,*N*,*N*′,*N*′-tetramethylethylene-diamine (TMEDA; 37.5 μL, 0.25 mmol) was added at rt followed by the addition of alkyl halide (0.75 mmol) and aryl bromide (0.25 mmol). The vial was closed and sealed with parafilm. The reaction was stirred vigorously at rt for 24 h. The reaction mixture was extracted with EtOAc (0.2 mL x 4) and filtered through a plug of silica gel. The crude product was purified by flash chromatography on silica gel.

4.8. General procedure for reductive aminations (Table 1, entries 14–16; Table 2, entry 4)

Pd/C (5.32 mg; 1 wt %; 2000 ppm, with respect to aldehyde) was added along containing a PTFE coated magnetic stir bar, to a 1-dram screw cap vial. An aldehyde (0.25 mmol) and an amine (1.2 or 1.5 equiv) were added to this vial. 0.5 mL 2 wt % surfactant/H_2O solution was then added prior to addition of 48 μL of triethylsilane (1.2 equiv). The vial was quickly closed with the screw cap and stirred at 45 °C for 3–4 h. The products were then separated by extraction with EtOAc (ca. 0.5 × 4 mL). The organic layer was adsorbed on silica and purified using flash column chromatography to afford the desired compound.

4.9. General procedure for S_NAr reactions (Table 1, entries 17–19; Table 2, entry 7)

A 1-dram reaction vial containing a PTFE coated magnetic stir bar, was charged with the $K_3PO_4.H_2O$ (69 mg, 0.3 mmol), the electrophile (0.25 mmol), and the nucleophile (0.275 mmol; via syringe if liquids). A 0.5 mL 2 wt % surfactant/H_2O solution was added via syringe. The reaction vial was screw capped and mixture was stirred vigorously at 45 °C for a given time. After completion, the reaction mixture was extracted with EtOAc (0.2 mL x 4) and filtered through a plug of silica gel. The crude product was purified by flash chromatography on silica gel.

4.10. General procedure for Suzuki-Miyuara couplings (Table 1, entries 20–21; Table 2, entry 1)

Into a 1-dram screw cap vial containing a PTFE coated magnetic stir bar was added 100 μL (for 300 ppm Pd, with respect to aryl/vinyl halide) of stock solution (Note: see SI for the preparation of stock solution) and the vial was covered with a rubber septum. The THF from this solution was evacuated under low pressure (~15 min). The aryl/vinyl halide (0.25 mmol; if solid or added after an evacuation/backfill sequence if liquid), 0.3 mmol boronic acid were added to this vial. The vial was evacuated and backfilled with argon (this procedure was repeated three times). A 0.5 mL 2 wt % surfactant/H_2O solution followed by Et_3N (1.0 mmol) were added under argon. The vial was quickly replaced with the screw cap and stirred at 45 °C for a given time. The products were then separated by either filtration, decantation of the aqueous layer, or extraction with a minimum amount of MTBE or EtOAc. The organic layer was adsorbed on silica and purified using flash column chromatography.

4.11. General procedure for nitro reductions (Table 1, entries 22–24)

Into a 1-dram screw cap open top vial containing a PTFE coated magnetic stir bar was added 10.6 mg 1 wt % Pd/C (4000 ppm, with respect to nitro compound) and a nitro compound (0.25 mmol). An aqueous solution 0.5 mL 2 wt % surfactant was then added into the reaction vial. The vial was closed and a TFE lined silicone SURE-LINK septa was punctured with needle (18 G) attached with pre-filled

balloon of hydrogen gas. The headspace of the vial was replaced with H_2 by unscrewing the cap under a positive H_2 flow for ca. 5 sec. and stirred at 45 °C for a given time. The products were then separated by extraction with EtOAc (ca. 0.5 × 4 mL). The organic layer was adsorbed on silica and purified using flash column chromatography to afford the desired compound.

4.12. General procedure for nitro reductions (Table 2, entry 6)

Into a 1-dram screw cap vial with a PTFE coated magnetic stir bar was added a nitro compound (0.25 mmol), carbonyl Fe powder (CIP; 5.0 equiv, 69.8 mg), and NH_4Cl (3.0 equiv, 40.3 mg) and 10 vol % THF (50 μL) as a co-solvent following the addition of 2 wt % TPGS-750-M/H_2O. The vial was screw capped and stirred at 45 °C for a given time. The product was then separated by extraction with EtOAc (ca. 0.5 × 4 mL), followed by filtration using short plug silica. The organic layer was adsorbed on silica and purified using flash column chromatography to afford the desired compound.

4.13. General procedure for Sonogashira couplings (Table 1, entries 25–26; Table 2, entry 2)

Into a 1-dram screw cap vial containing a PTFE coated magnetic stir bar, 100 μL of stock solution (1000 ppm palladium) or 150 μL of stock solution (1500 ppm palladium, with respect to aryl bromide) was added (Note: see SI for the preparation of catalyst stock solution) and the THF was removed in vacuo, after which the reaction vial was backfilled with dry argon. Aryl bromide (0.25 mmol) and terminal alkyne (0.3 mmol) if solids, or added after an evacuation/backfill sequence and 0.5 mmol $K_3PO_4.H_2O$ was added into a reaction vial. The reaction vial was then evacuated and backfilled with argon (repeated three times). A 0.5 mL 2 wt % surfactant/H_2O solution was then added. The reaction mixture was then stirred vigorously at 45 °C for a given time. After reaction completion, the reaction mixture was extracted with EtOAc (0.5 mL x 3). The crude product was purified by flash chromatography over silica gel to afford pure product.

4.14. General procedure for Stille couplings (Table 1, entries 27–28)

Into a 1-dram reaction vial containing a PTFE coated magnetic stir bar, were added aryl halide (0.25 mmol), NaCl (15 mg, 0.25 mmol), stannyl reagent (0.275 mmol, if solid), Pd(*t*-$Bu_3P)_2$ catalyst (2.6 mg, 2 mol %, with respect to aryl halide) and DABCO (82.5 μL, 0.75 mmol). The reaction vial was evacuated and refill with argon (repeated 3 times). Under positive argon flow, 0.5 mL of 2 wt % surfactant/H_2O solution was added. The mixture was allowed to stir vigorously for a given time at room temperature. The reaction mixture was extracted with (0.5 mL x 3) of EtOAc. The crude product was purified by flash chromatography on silica gel.

4.15. General procedure for Fe/ppm Pd NPs catalyzed Suzuki-Miyaura couplings (Table 1, entry 29; Table 2, entries in 8)

Into a 1-dram screw cap vial containing a PTFE coated magnetic stir bar, boronic acid (0.24 mmol), $K_3PO_4.H_2O$ (69.2 mg, 0.3 mmol) and Fe/ppm Pd NPs (8 mg, 350 ppm Pd, with respect to aryl halide) were added following the addition of 0.4 mL 2 wt % surfactant/H_2O. The mixture was stirred at rt under argon for 1–2 min, after which addition of aryl halide (0.2 mmol) was done. The reaction mixture was heated at 45 °C for 24 h, and after completion the reaction mixture was extracted with ethyl acetate (2 mL x 3). The crude product was purified by flash chromatography on silica gel.

4.15.1. 2′,3′-difluoro-[1,1′-biphenyl]-3-carbonitrile

White solid, 37.5 mg, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.25–7.14 (m, 3H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 152.2, 149.0, 136.1, 133.4, 132.6, 131.8, 129.6, 129.1, 125.2, 124.7, 118.6, 117.5, 113.1. HRMS (ESI+) calcd for $[C_{13}H_7F_2N]^+$ 215.0547; found 215.0544.

4.16. General procedure for Fe/ppm Pd NPs catalyzed Heck couplings (Table 2, entries in 9)

Into a 1-dram screw cap vial containing a PTFE coated magnetic stir bar, aryl iodide (0.2 mmol), K_3PO_4•H_2O (127.4 mg, 0.6 mmol), NaCl (70.2 mg, 1.2 mmol) and Fe/ppm Pd NPs (5.5 mg, 1000 ppm Pd, with respect to aryl iodide) were added following the addition of 0.4 mL 2 wt % surfactant/H_2O. The resulting mixture was stirred at rt under argon for 1–2 min, after which addition of alkene (0.4 mmol) was done and the reaction mixture was stirred at rt for 12 h. After reaction completion, the mixture extracted with ethyl acetate (2 mL x 3). The crude product was purified by flash chromatography on silica gel; **ethyl (*E*)-3-(3-((2-ethylhexyl)oxy)-3-oxoprop-1-en-1-yl)benzoate**. Yellow oil, 65.2 mg, 98% yield. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.27–8.17 (m, 1H), 8.10–8.01 (m, 1H), 7.76–7.65 (m, 2H), 7.52–7.42 (m, 1H), 6.59–6.48 (m, 1H), 4.47–4.35 (m, 2H), 4.20–4.09 (m, 2H), 1.67 (m, 1H), 1.48–1.29 (m, 11H), 0.98–0.89 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 166.1, 143.4, 134.9, 132.2, 131.3, 131.1, 129.1, 129.1, 119.7, 67.2, 61.4, 39.0, 30.6, 29.1, 24.0, 23.1, 14.4, 14.2, 11.2. HRMS (ESI+) calcd for $[C_{20}H_{28}O_4]^+$ 332.1988; found 332.1955.

4.16.1. (E)-2-(4-(1H-pyrrol-1-yl)styryl)pyridine

Yellow solid, 46.8 mg, 95% yield. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.62 (d, J = 4.1 Hz, 1H), 7.72–7.59 (m, 4H), 7.45–7.33 (m, 3H), 7.21–7.09 (m, 4H), 6.46–6.29 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 149.8, 140.5, 136.7, 134.1, 131.8, 128.4, 127.9, 122.3, 122.2, 120.5, 119.2, 110.8. HRMS (ESI+) calcd for$[C_{17}H_{13}N_2]^+$ 245.10798; found 245.1073.

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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Appendix A. Supplementary data

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References

[1] (a) B.H. Lipshutz, J. Org. Chem. 82 (2017) 2806–2816;
(b) B.H. Lipshutz, F. Gallou, S. Handa, ACS Sustain. Chem. Eng. 4 (2016) 5838–5849.
[2] (a) C.-J. Li, L. Chen, Chem. Soc. Rev. 35 (2006) 68–82;
(b) T. Kitanosono, K. Masuda, P. Xu, S. Kobayashi, Chem. Rev. 118 (2018) 679–746;
(c) D.K. Romney, F.H. Arnold, B.H. Lipshutz, C.-J. Li, J. Org. Chem. 83 (2018) 7319–7322;
(d) F.H. Arnold, Angew. Chem. Int. Ed. 57 (2018) 4143–4148. Angew. Chem. 130 (2018) 4212–4218.
[3] (a) B.H. Lipshutz, Curr. Opin. Green Sustainable Chem. 11 (2018) 1–8;

(b) G. La Sorella, G. Strukul, A. Scarso, Green Chem. 17 (2015) 644–683;
(c) T. Dwars, E. Paetzold, G. Oehme, Angew. Chem. Int. Ed. 44 (2005) 7174–7199. Angew. Chem. 117 (2005) 7338–7364.

[4] M.P. Andersson, F. Gallou, P. Klumphu, B.S. Takale, B.H. Lipshutz, Chem. Eur J. 24 (2018) 6778–6786.

[5] (a) For PTS, see B.H. Lipshutz, B.R. Taft, Org. Lett. 10 (2008) 1329–1332. Lipshutz, B. H.; Petersen, T. B.; Abela, A. R. Org. Lett. 10 (2008) 1333–1336; Lipshutz, B. H.; Abela, A. R. Org. Lett. 10 (2008) 5329–5332; Lipshutz, B. H.; Chung, D. W.; Rich, B. Org. Lett. 10 (2008) 3793–3796;
(b) B.H. Lipshutz, S. Ghorai, A.R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R.D. Gaston, R.C. Gadwood, J. Org. Chem. 76 (2011) 4379–4391;
(c) P. Klumphu, B.H. Lipshutz, J. Org. Chem. 79 (2014) 888–900;
(d) N.R. Lee, M. Cortes-Clerget, A.B. Wood, D.J. Lippincott, H. Pang, F.A. Moghadam, F. Gallou, B.H. Lipshutz, ChemSusChem 12 (2019) 3159–3165;
(e) M. Cortes-Clerget, S.E. Spink, G.P. Gallagher, L. Chaisemartin, E. Filaire, J.-Y. Berthon, B.H. Lipshutz, Green Chem. 21 (2019) 2610–2614.

[6] (a) J. Brals, J.D. Smith, F. Ibrahim, F. Gallou, S. Handa, ACS Catal. 7 (2017) 7245–7250;
(b) D. Petkova, N. Borlinghaus, S. Sharma, J. Kaschel, T. Linder, J. Klee, A. Jolit, V. Haller, S. Heitz, K. Britze, J. Dietrich, W.F. Braje, S. Handa, ACS Sustain. Chem. Eng. 8 (2020) 12612–12617.

[7] Y. Yang, X. Meng, B. Zhu, Y. Jia, X. Cao, S. Huang, Eur. J. Org Chem. (2019) 1166–1169.

[8] C. Krell, R. Schreiber, L. Hueber, L. Sciascera, X. Zheng, A. Clarke, R. Haenggi, M. Parmentier, S. Rodde, H. Baguia, J. Keusch, F. Gallou, Waste water from α-tocopherol derived surfactant chemistry: risk or opportunity? Org. Process Res. Dev. (2021) https://doi.org/10.1021/acs.oprd.0c00547.

[9] (a) J. Kostal, A. Voutchkova-Kostal, P.T. Anastas, J.B. Zimmerman, Proc. Natl. Acad. Sci. Unit. States Am. 112 (2015) 6289–6294;
(b) A.M. Voutchkova, J. Kostal, J.B. Steinfeld, J.W. Emerson, B.W. Brooks, P.T. Anastas, J.B. Zimmerman, Green Chem. 13 (2011) 2373–2379.

[10] F. Melnikov, J. Kostal, A. Voutchkova-Kostal, J.B. Zimmerman, P.T. Anastas, Green Chem. 18 (2016) 4432–4445.

[11] (a) . https://www.lhasalimited.org/products/sarah-nexus.htm. (Accessed 10 January 2021);
(b) . https://www.scienceexchange.com/labs/multicase-inc. (Accessed 10 January 2021).

[12] (a) T. Yu, H. Pang, Y. Cao, F. Gallou, B.H. Lipshutz, Angew. Chem. Int. Ed. (2020), https://doi.org/10.1002/anie.202013017;
(b) N. R. Lee, F. A. Moghadam, F. C. Braga, D. J. Lippincott, B. Zhu, F. Gallou, B. H. Lipshutz, 22 (2020) 4949–4954. (c) A.B. Wood, M. Cortes-Clerget, J.R.A. Kincaid, B. Akkachairin, V. Singhania, F. Gallou, B.H. Lipshutz, Angew. Chem. Int. Ed. 59 (2020) 17587–17593;
(d) H. Pang, Y. Wang, F. Gallou, B.H. Lipshutz, J. Am. Chem. Soc. 141 (2019) 17117–17124;
(e) S. Handa, M.P. Andersson, F. Gallou, J. Reilly, B.H. Lipshutz, Angew. Chem. Int. Ed. 55 (2016) 4914–4918;
(f) M. Cortes-Clerget, N.R. Lee, B.H. Lipshutz, Nat. Protoc. 14 (2019) 1108–1129;
(g) N.R. Lee, A.A. Bikovtseva, M. Cortes-Clerget, F. Gallou, B.H. Lipshutz, Org. Lett. 19 (2017) 6518–6521.

[13] (a) B.H. Lipshutz, G.T. Aguinaldo, S. Ghorai, K. Voigtritter, Org. Lett. 10 (2008) 1325–1328;
(b) Y. Zhang, B.S. Takale, F. Gallou, J. Reilly, B.H. Lipshutz, Chem. Sci. 10 (2019) 10556–10561;
(c) B.S. Takale, R.R. Thakore, E.S. Gao, F. Gallou, B.H. Lipshutz, Green Chem. 22 (2020) 6055–6061;
(d) B.H. Lipshutz, S. Ghorai, A.R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R.D. Gaston, R.C. Gadwood, J. Org. Chem. 76 (2011) 4379–4391;
(e) R.R. Thakore, B.S. Takale, G. Casotti, E.S. Gao, H.S. Jin, B.H. Lipshutz, Org. Lett. 22 (2020) 6324–6329;
(f) N.A. Isley, R.T.H. Linstadt, S.M. Kelly, F. Gallou, B.H. Lipshutz, Org. Lett. 17 (2015) 4734–4737;
(g) B.S. Takale, R.R. Thakore, S. Handa, F. Gallou, J. Reilly, B.H. Lipshutz, Chem. Sci. 10 (2020) 8825–8831;
(h) R. R. Thakore, B. S. Takale, X. Li, F. Gallou, B. H. Lipshutz, Unpublished Work. (i) B. Jin, F. Gallou, J. Reilly, B.H. Lipshutz, Chem. Sci. 10 (2019) 3481–3485;
(j) G.-P. Lu, C. Cai, B.H. Lipshutz, Green Chem. 15 (2013) 105–109.

[14] (a) R.R. Thakore, B.S. Takale, V. Singhania, F. Gallou, B.H. Lipshutz, ChemCatChem 13 (2021) 212–216;
(b) E. Landstrom, N. Akporji, C.M. Gabriel, N.R. Lee, F.C. Braga, B.H. Lipshutz, Org. Lett. 22 (2020) 6543–6546;
(c) B.S. Takale, R.R. Thakore, N.M. Irvine, A. Schuitman, X. Li, B.H. Lipshutz, Org. Lett. 12 (2020) 4823–4827;
(d) N. Akporji, R.R. Thakore, M. Cortes-Clerget, J. Anderson, E. Landstrom, D.H. Aue, F. Gallou, B.H. Lipshutz, Chem. Sci. 11 (2020) 5205–5212;
(e) B.S. Takale, R.R. Thakore, R. Mallarapu, F. Gallou, B.H. Lipshutz, Org. Process Res. Dev. 24 (2019) 101–105;
(f) B.S. Takale, R.R. Thakore, F.Y. Kong, B.H. Lipshutz, Green Chem. 21 (2019) 6258–6262;
(g) R.R. Thakore, B.S. Takale, F. Gallou, J. Reilly, B.H. Lipshutz, ACS Catal. 12 (2019) 11647–11657.