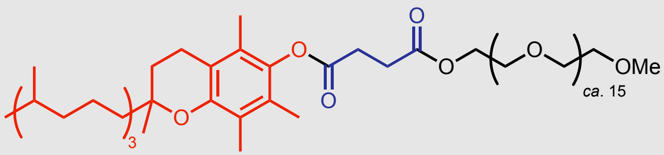
POTW: TPGS-750-M/H_2O in organic synthesis

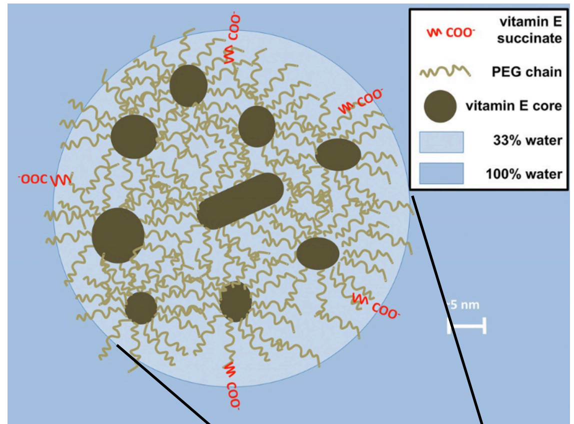
TPGS-750-M:



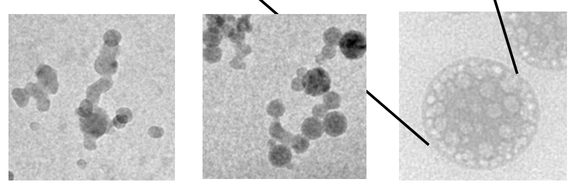
lipophilic component: α-tocopherol/vitamin E — diester linker: 4-carbon — PEG chain: PEG-750-M

- Inspired by PTS (10-carbon diester with PEG-600): developed as a water-soluble form of VE, shown to improve bioavailability of CoQ_{10}, an antioxidant for cells, by carrying it in nanomicelles — potential as a surfactant?
- Early screening of commertially available nonionic surfactants in water on olefin cross-metathesis: PTS gives superior results and was found to form larger nanomicelles (ca. 20 nm, among other sizes) — correlation?
- Synthesis: formation of unsymmetrical diester most selective with cyclic anhydride and monomethylated PEG
- TPGS-750-M consistently gave the best results in a series of tested reactions; DLS and cryo-TEM revealed that it only formed spherical micellar nanoparticles (ca. 50-60 nm, while micelles >150 nm can be heterogenous)
- Longer PEG chain, greater internal coiling, allowing fewer molecules to be accommodated per nanomicelle (smaller micelles)

Proposed structure for TPGS-750-M nanomicelle:



Cryo-TEM images:



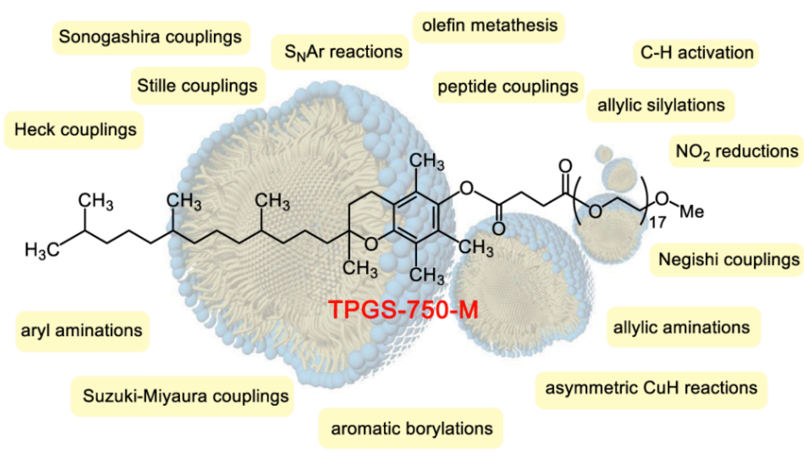
Brij-30 — *TPGS-1000-M* — *TPGS-750-M*

Comments on the proposed structure:
- TPGS-750-M has impurities in the range 1-5mol% that consist mainly of VE, VE succinate, uncapped surfactant and surfactant dimer
- Deprotonated VE succinate effectively reduces interfacial tension (IFT) to ~0 (system doesn't gain free energy via decreasing surface area between the phases), and thus stabilizing nanomicelles formed
- DLS measurements for diameters of nanomicelle at low pH = 46 nm, at high pH = 24 nm
- 50 nm is far too large for a nanoparticle to be a single micelle (~10 nm); proposal of a multi-micelle nanoparticle, supported by cryo-TEM image, explains the increased yields observed

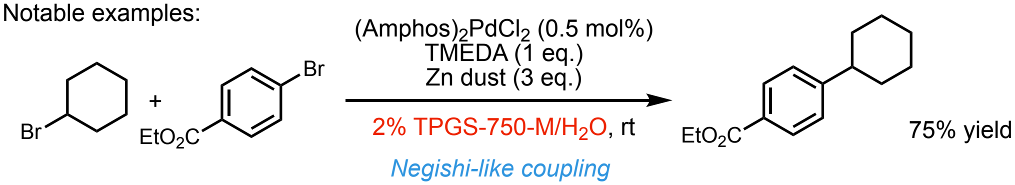
General features of nanomicelles:
- Arrays are dynamic
- Formation driven by entropy upon addition of water at above critical micelle concentration (CMC)
- Concentrations within a nanomicelle are ca. 10x those commonly used in organic media, which in combination with proper shape and size can give competitive reaction rates under mild conditions
- How and why certain features facilitate synthetic chemistry in nanomicelles are largely unknown

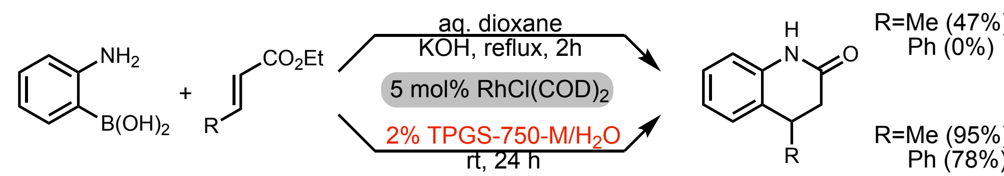
JOC **2011**, 76, 4379.
JOC **2017**, 82, 2806-2816.
Chem. Eur. J. **2018**, 24, 6778-6786.

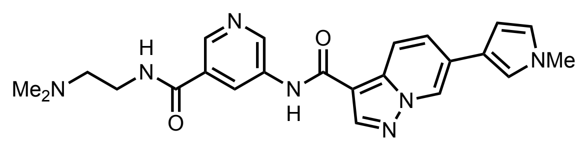
Representative types of reactions run in aq. TPGS-750-M:



Notable examples:



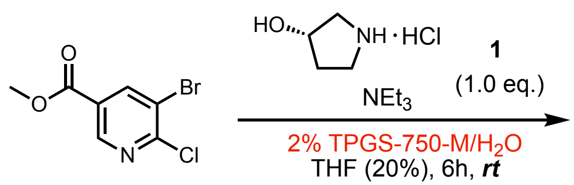




Novartis, ca. 10g scale
Conditions: 2% TPGS-750-M/H_2O, THF (20%)

POTW: TPGS-750-M/H_2O in organic synthesis

First kilogram scale process that applies surfactant technology: *Green Chem.* **2016**, 18, 14-19.; *Nat. Rev. Chem.* **2018**, 2, 306-327.

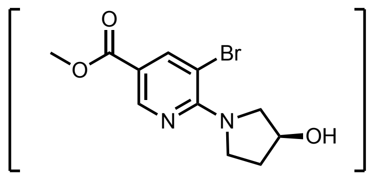


1 (1.0 eq.)

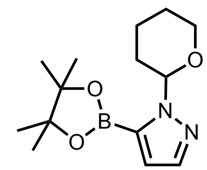
NEt_3

2% TPGS-750-M/H_2O
THF (20%), 6h, ***rt***

S_NAr



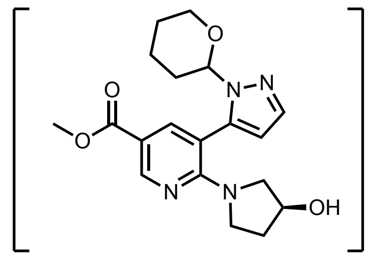
86% yield



2 (1.0 eq.)

2% TPGS-750-M/H_2O
THF (15%), $PdCl_2$(dtbpf) (2 mol%)
NEt_3, 4h, ***rt***

Suzuki-Miyaura reaction



S_NAr: THF prevents oiling out and is distilled off to directly precipitate out the desired product in high purity

vs. **1** (1.2 eq.) in i-PrOH/PhMe, 80°C: 87% yield
- Minor amount of O-arylated product: can be removed via recrystallization; can be reduced with using 1.4 eq. **1** at the cost of less conversion; can be reduced with lower temperature at the cost of longer cycle time

Suzuki: Hydrolyzed product obtained in excellent purity (>98%) via direct precipitation

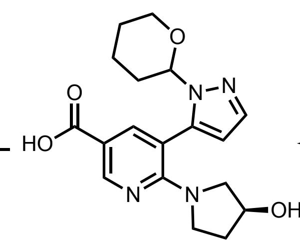
vs. **2** (1.4-1.5 eq.) in t-AmOH, 85°C: 60% yield after hydrolysis
- Requires rather high loading of Pd cat.: tedious downstream removal

Amidation: PEG prevents oiling out; uncapped PEG200 gives the best selectivity and kinetic profile — ca.1% O-acylation side product

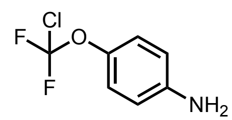
vs. **3** (1.2 eq.) in MeCN, 50°C: 76% yield, 12% O-acylation side product

NaOH, MeOH
2h, ***rt***

Hydrolysis



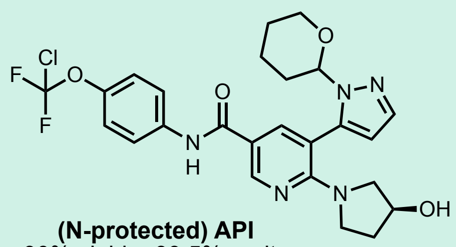
90% yield over 2 steps



3 (1.0 eq.)

2% TPGS-750-M/H_2O
uncapped PEG200 (20%)
EDCI, HOBTNMM
10h, ***rt***

Amide bond formation

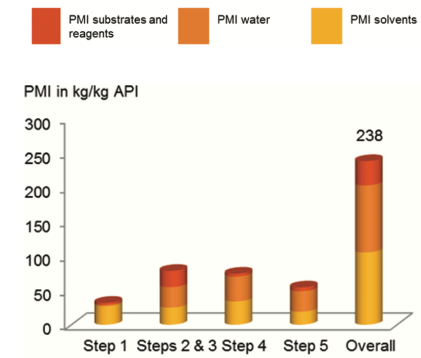


(N-protected) API
90% yield, >99.5% purity

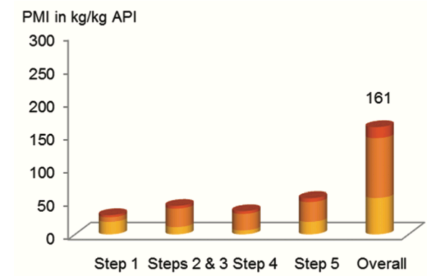
- ***Mild conditions***: preserve desired reactivity, minimize/avoid undesired pathways
- Surfactant: "benign by design", 0.15% allowance in API that's very easily achieved
- Metal residual: substantial depletion

(The API, Asciminib, is currently undergoing clinical studies in chronic myelogenous leukemia (CML) patients.)

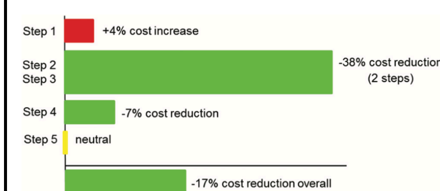
Evaluation of efficiency based on PMI, cost and cycle time:



a) process in organic solvents



b) process in water with surfactants



Step	Cycle time (h) Organic solvent	TPGS-750-M/water
S_NAr to **3**	104	61
Cross-coupling to **5**	61	24
hydrolysis to **6**	137	53
Amide-bond formation to **8**	105	76
Final deprotection to API	62	62
Total	469 (19.5 days)	276 (11.5 days)