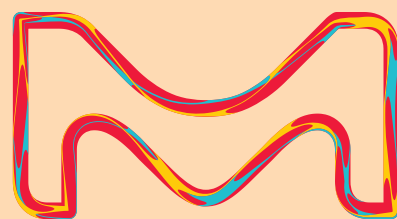
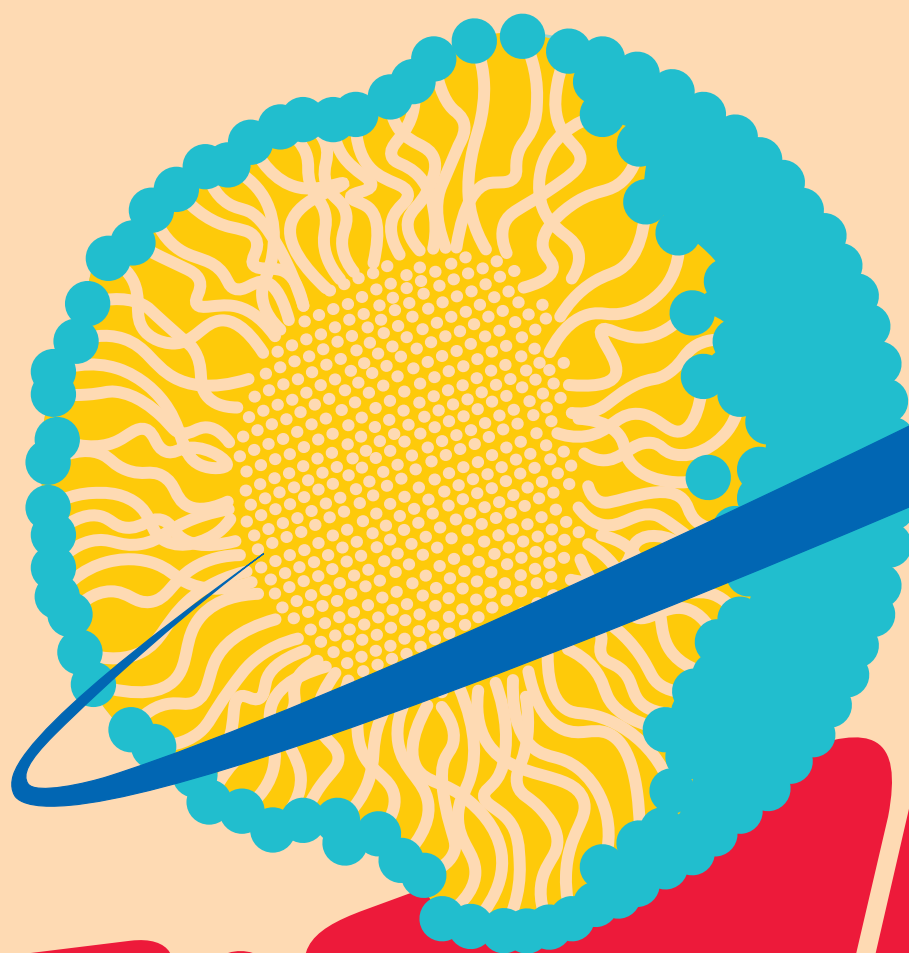


Utilizing Micellar Catalysis for Organic Synthesis: A Desk Reference



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Forward

Chemists reach for a bottle of organic solvent for every reaction, because, well, historically it works—organic solvents get the job done. Unfortunately, this propagates unsustainable practices throughout our community. Organic solvents are toxic and oftentimes flammable. My goal in writing this Guide/Desk Reference is to convince the reader to try a safer, more sustainable medium—water. Water, when used with small amounts of a newly engineered surfactant, often produces great clean results.

The Lipshutz group over the past 12 years has developed sustainable, practical and user-friendly synthesis methodologies. These advances follow the 12 Principles of Green Chemistry. They aim to (1) remove organic solvents from organic reactions using environmentally friendly surfactants in water; (2) recycle the catalyst, water, and surfactant; (3) run reactions under mild conditions, typically at ambient temperatures; (4) minimize waste due to reaction workup and purification (leading to low E Factors/PMI); and (5) lower catalyst loadings, especially involving platinoids, to ppm levels, given their endangered status. Using water as the bulk reaction medium along with very limited amounts of a re-usable “designer” surfactant enables the realization of these goals.

Given the novelty of this approach, I’ve encountered many chemists ‘on the fence’ or intimidated by seeing 2 wt % of some surfactant under a reaction arrow. During my time in the Lipshutz group, I used micellar catalysis and became familiar with not only setting up reactions using this technology, but also troubleshooting. Additionally, I spent 6 months working with process chemists within the CHemical & Analytical Development (CHAD) department at Novartis in Basel, demonstrating the applicability of micellar catalysis to ‘real-world’ active pharmaceutical ingredients (APIs). Within CHAD, these interactions focused primarily on answering their questions and ‘hang-ups’ regarding micellar catalysis. This chemistry was not only amenable to kilogram-scale synthesis of an API, it lowered their PMI, reduced costs, and allowed Novartis to make an API in half the time needed using traditional methods.

Hopefully, this contribution addresses many common questions by chemists in both academia and industry. It should serve as a “one-stop shop” for key references, while functioning as a go-to guide with tips and tricks about reaction setup of every scale. After spending five years in the Lipshutz group, I have no doubt that micellar catalysis will occupy a prominent place among “green” alternatives available to the synthetic organic chemistry community. It already has been adopted by process chemists at Novartis and medicinal chemists at AbbVie. Meanwhile, many additional companies are now playing with this approach, which is bringing breakthroughs in green chemistry closer than ever. After all, there is no downside to this chemistry. I hope that after ‘thumbing’ through this guide you, too, will be eager to try this chemistry.

Nicholas A. Isley, Ph.D.



About the Author: Nicholas A. Isley received his B.S. from Western Washington University (2010). After exposure to research in organometallic chemistry as an undergraduate, he continued his education, taking his Ph.D. at the University of California, Santa Barbara (2015). Working with Bruce H. Lipshutz, he developed organic and organometallic reactions in water, applying micellar catalysis enabled by benign “designer” surfactants. In 2015, he moved to San Diego for postdoctoral studies with Professor Dale Boger at The Scripps Research Institute to gain experience in both medicinal chemistry and natural product total synthesis.

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Section 1: Overview

i. Why is micellar catalysis so attractive?

Key advantages:

- Amenable to milligrams or kilograms
- Utility in medicinal and process chemistry
- Simplified reaction setup, workup and purification
- Mild conditions (22-45 °C)
- 1 to 1 stoichiometry of reactants
- Low catalyst loading (ppm)
- One-pot, multistep chemistry
- Higher yields compared to those in organic solvents
- Catalyst and surfactant recycling
- Reduction in waste (E Factor/PMI)
- Substitution for polar, aprotic solvents
- Minimal number of technical operations

ii. Applications to medicinal chemistry

Utility in medicinal chemistry at AbbVie:

Medicinal chemists typically want a fast and easy way to make many compounds. Since their goal is to answer biological questions, medicinal chemists often do not care about yields if they can answer these questions quickly and easily. Despite this, AbbVie's medicinal chemistry department has adapted micellar catalysis into their workflow to synthesize medically relevant molecules (Figure 1). They have found chemistry in water to be not only cleaner and higher yielding, but also sometimes succeeding in cases where organic solvents have failed.

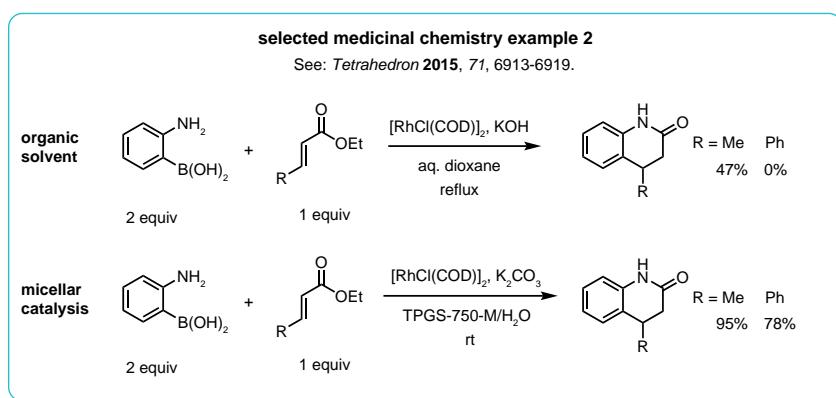
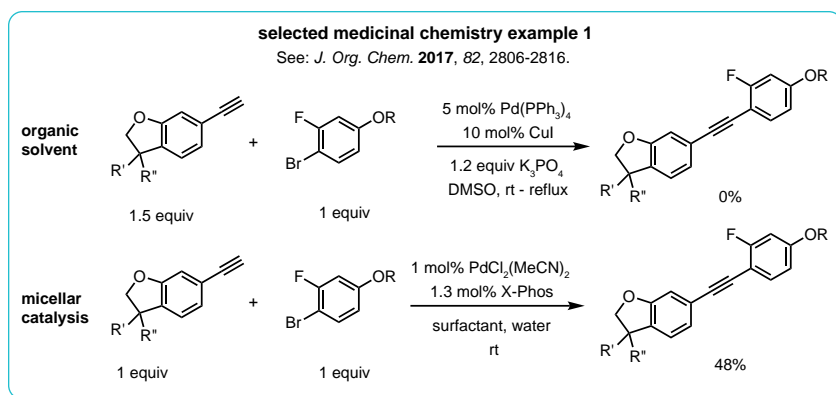


Figure 1. AbbVie's comparative examples of using organic solvent vs. micellar catalysis to synthesize medically relevant small molecules.

"Never in my twenty years as a medicinal chemist has a new technology worked as advertised on the first try again and again."

Wilfried M. Braje, Ph.D.,
Senior Principal Scientist
AbbVie

Utility in process chemistry at Novartis:

Process chemists within the CHemical & Analytical Development (CHAD) department at Novartis in Basel have been synthesizing complex small molecules by minimizing or completely avoiding toxic solvents. They demonstrated the feasibility of micellar catalysis, at scale, on a six-step process using TPGS-750-M (2 wt %) in water that was operationally simple and utilized in-house equipment. Notable achievements include: raw material cost reduction of ca. 17%, a PMI reduction of 31%, and by minimizing operational time, a two-fold increase in throughput (Figure 2).¹ Novartis has additionally been working with the Lipshutz group due to their interest in combining recently developed nanoparticle-catalyzed reactions using micellar catalysis that can achieve ppm levels of catalyst loading,² to further reduce costs.

6-step route to an API		
	organic solvents vs. micellar catalysis	
# of technical operations ^a	40	25
# of organic solvents	9	1 (MeOH)
purity	>99.0%	>99.5%
total yield (6 steps)	47% (optimized)	47% (unoptimized)
productivity (normalized)	1	1.7
PMI	236	161
cycle time (h)	469 (19.5 days)	276 (11.5 days)

^a operation = reaction setup, washing, extraction, filtration, or drying

Summary of advantages after switching to micellar catalysis

- improved process performance
 - reduction of organic solvents
 - reduction of cycle time
 - milder reaction conditions
 - reduction in PMI
 - reduction of raw materials
 - reduction of cost
- to name a few...

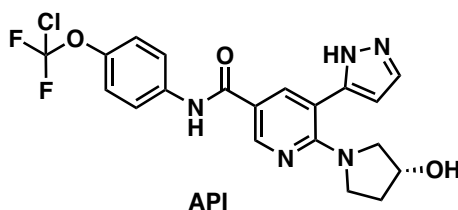


Figure 2. Comparative analysis of a six-step process performed in solvent vs. micellar catalysis.

"It internally triggered a paradigm shift that has since contributed to a more systematic evaluation and implementation of the technology on scale..."

Fabrice Gallou, Ph.D.,
Principal Fellow and Leading Scientist
Novartis

iii. Micellar catalysis as an alternative medium to toxic solvents (e.g., polar, aprotic solvents):

The use of polar, aprotic solvents for substitution reactions such as S_NAr or S_N2 reactions and peptide synthesis are common. From a recent survey, within a 16 year period, nearly 50% of DMF, DMAc, NMP, and DMSO (Figure 3) usage was due to substitution reactions alone.³ Due to DMF's CMR properties (carcinogenic, mutagenic or toxic to reproduction), the European Chemical agency labeled DMF as a substance of high concern, forcing many industrial labs to find alternatives. Reports from the Lipshutz group and further developed by Novartis have demonstrated that such reactions can take place using micellar catalysis, avoiding these toxic solvents for both S_NAr ⁴ and peptide bond-forming⁵ reactions on scale.⁶

Use micellar catalysis to replace DMF and other polar, aprotic solvents. See:

Org. Lett. **2015**, *17*, 4734.

Org. Process Res. Dev. **2016**, *20*, 1104.

Org. Process Res. Dev. **2016**, *20*, 1388.

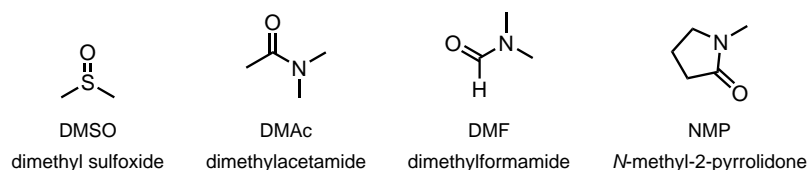


Figure 3. Using micellar catalysis to replace CMR (carcinogenic, mutagenic or toxic to reproduction) solvents deemed by REACH (Registration, Evaluation, Authorization and Restriction of Chemicals).

For additional information about AbbVie's and Novartis' experience with micellar catalysis, see below:

Video seminar:

<https://www.chemistryworld.com/1017569.article>

An "Inside View" interview with Fabrice Gallou:

<https://www.nature.com/advertorials/insideview/pdf/ivsigmajune2016.pdf>

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Section 2: User Guide

i. Introduction to micellar catalysis

General Introduction

The term “micellar catalysis” can be a misnomer, as micelles typically do not catalyze a reaction. Instead it refers to a solution that contains a catalytic amount of a surfactant, which forms micelles above a certain concentration in water (i.e., the critical micelle concentration, or CMC). The surfactant, generally, does not participate in the reaction, instead it aids in solubilizing organic compounds. Depending on the surfactant, the micelles formed differ in both shape and size. This is an important parameter for reaction conversion and, ultimately, yields—a difficult-to-predict parameter. Empirically, both spherical and worm-like nanoparticles between 40–65 nm which are aggregates of micelles result in the best yields, exhibit a large reaction scope, and translate to many reaction types. These “designer” surfactants consist of three structural components: a lipophilic portion, a linker, and a hydrophilic tail, which spontaneously form micelles upon dissolution in water. Reactions typically occur at room temperature and exhibit faster rates compared to those observed using traditional organic solvents, due to a high localized concentration within the lipophilic core. The core of the micelle acts as the organic solvent; this is where reactions take place (Figure 1).

For a recent ACS webinar by Bruce Lipshutz: acs.org/content/acs/en/acs-webinars/technology-innovation/water-chemistry

What is the role of the surfactant?

The surfactant aids in solubilizing the otherwise water-insoluble organic compounds that are necessary for a given transformation. In some cases it even catalyzes the reaction. Many compounds, reagents, and catalysts in small-molecule synthesis are minimally soluble in water. Therefore the surfactant ‘tricks’ organic compounds into dissolving in a highly concentrated fashion within the lipophilic core of the micelle.* Typically, the resulting mixture is between homogeneous and heterogenous, and best thought of as a micro-emulsion. Reaction mixtures often appear milky throughout the course of the reaction.

*Occasionally, reactions work equally well or better without the surfactant (i.e., on water). In general, however, the surfactant is key to creating a consistent environment necessary for both high reaction yields, consistent reaction monitoring, and scalability.

Clarification of common terms used within the literature:

The terms “surfactant” and “amphiphile” are often used interchangeably in micellar catalysis publications since the surfactant possesses both a lipophilic and hydrophilic component. “Nanomicelles”, “micelles”, and “nanoreactors” tend to be used interchangeably. All refer to micelles that are formed in an aqueous medium where the reaction takes place. The term “in water” refers to any reaction that takes place in the surfactant solution within the core or interface of a micelle. This is different from an “on water” reaction, which does not utilize a surfactant (i.e., water is the bulk medium), and in this case, the reaction is occurring on the surface of water, hence “on water.”

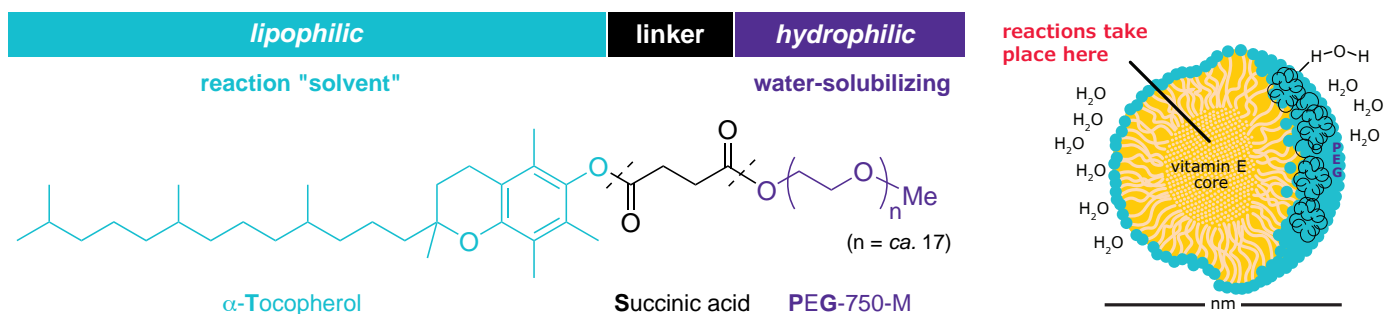


Figure 1. Structure of “designer” surfactant TPGS-750-M and its three main components (left). Pictogram of micelles dissolved in water (right).

ii. Choosing/preparing your surfactant solution

Different types of surfactants are commercially available and have been used for successful micellar catalysis (Figure 2). The three most general surfactants are PTS,¹ TPGS-750-M² and Nok.³ Other "designer" surfactants such as PQS⁴ can tether precious metals for recycling purposes allowing, e.g., asymmetric Rh-catalyzed 1,4-additions,⁵ Grubbs metathesis chemistry,⁶ and visible-light iridium photoredox catalysis.⁷ Commercially available surfactants such as Tween, Triton X, and Brij also work, although are less general. Given the large number of reactions developed using TPGS-750-M, this is the most recommended surfactant. The Nok surfactant is less general, but a cheaper alternative and often gives comparable yields to TPGS-750-M.

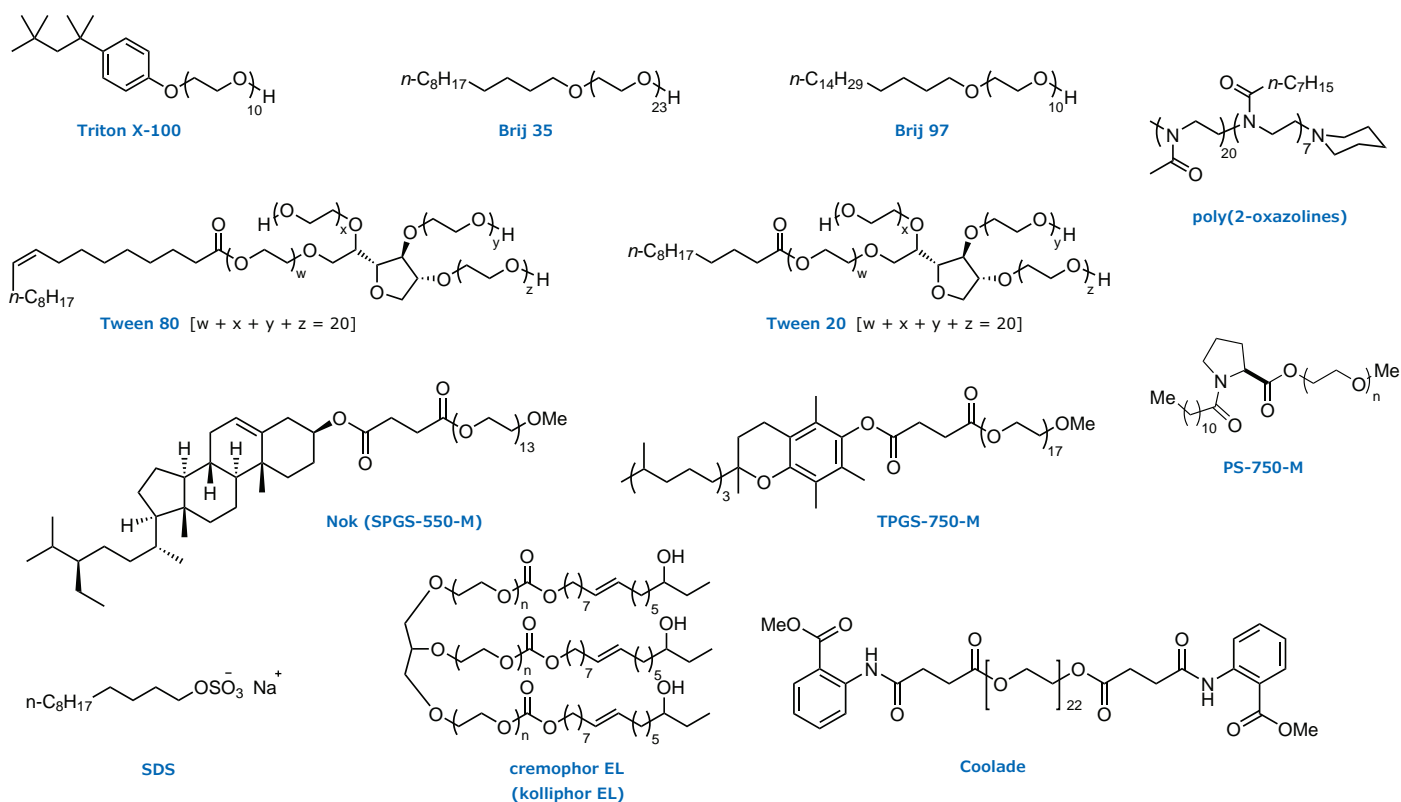


Figure 2. Representative surfactants that are commercially available.

Preparation of a surfactant solution (solutions commercially available through Sigma-Aldrich.com):

The desired wt % of surfactant is added to a vessel equipped with a stir bar intended for long-term storage either in a round-bottom flask with a septum or a vial with a crimp-top. If your reactions are sensitive to air, this vessel should be placed under high-vacuum and back-filled with argon or nitrogen. This process is repeated 3-5 times. In a separate vessel, HPLC grade water is degassed by sparging for several hours under a stream of argon or nitrogen, followed by evacuating the flask and back-filling it with argon or nitrogen (repeated 3-5 times). Alternatively, but less effectively, the water can be degassed by sparging for several hours under a stream of argon or nitrogen.

Next, degassed water is added to the vessel containing the surfactant and stirred at room temperature for several hours until the solution is homogeneous. Depending on the volume, overnight stirring may be necessary. The resulting surfactant solution can be stored for months (> 6 months) without loss in activity at room temperature under an inert atmosphere. Typically, the solution is kept under positive pressure with argon or nitrogen in case of future air-sensitive reactions. Treat this solution exactly as a bottle containing organic solvent. This surfactant solution can be removed by syringe and transferred to any reaction vessel. If your reactions are not sensitive to air, the same procedure applies, omitting degassing.

Note: Re-degassing the surfactant solution is possible, but remaking the solution is recommended. Sparging argon or nitrogen through a solution to re-degas works, but a lot of bubbling/frothing will occur. This will rise to the head-space and froth out at the puncture point. It is recommended that water be degassed before you dissolve the surfactant.

Concentration of the surfactant solution:

A 2 wt % solution of the surfactant is common for most reactions and is a recommended starting point. Concentrations as low as 1 wt % and as high as 15 wt % have been reported from the Lipshutz group.

Where do I begin?

- start with 2 wt % TPGS-750-M/H₂O for your surfactant solution

Product Discription	Product Number
Triton™ X-100	X100
Brij® 35	8.01962
TWEEN® 20	P1379
TWEEN® 80	P1754
TWEEN® 80 solution	P8192
SPGS-550-M	776033
TPGS-750-M (2 wt. % in H ₂ O)	733857
TPGS-750-M (5 wt. % in H ₂ O)	763918
TPGS-750-M	763896
Sodium dodecyl sulfate	436143
Kolliphor® EL	C5135
Ultroxa®: Poly(2-methyl-2-oxazoline) piperazine terminated	900358
PS-750-M solution	911178
PS-750-M	911151
Coolade	907014
Coolade solution	909793

iii. Reaction setup (small scale)

Equipment required: reaction vessel, magnetic stir bar, open cap with PTFE insert or septum

Vessels including round-bottom flasks, microwave vials, and disposable vials have been used for small scale reactions. The latter two are the most effective as they allow for the appropriately sized stir bar, which extends across the bottom of the vessel. Using a stir bar in this configuration allows for vigorous mixing. Be conscious to not use a vessel where the stir bar will not create a large vortex.



Insider knowledge:

- The common reaction concentration is 0.5 M. Rare, but as high as 2 M has been demonstrated. Too high a concentration of surfactant results in a very viscous solution and leads to inconsistent conversion due to the low volume of water.
- Vigorous stirring is key for this chemistry! Avoid splashing the reactants above the solvent level. Often the vortex extends to the bottom of the vessel, making the central area of your stir bar visible and exposed to the head-space throughout the reaction.
- Depending on the contents of the reaction mixture, if stirring is stopped, a biphasic solution will form immediately or may take 30+ minutes. For reaction monitoring, it is best to remove an aliquot while the reaction is stirring.
- Occasionally, 'clumping' slowly occurs over the course of the reaction. However, the overall level of conversion often remains high if you follow through with the workup and analysis.
- Typically, the resulting reaction mixture is somewhere between homogeneous and heterogeneous. It is best to think of the mixture as a micro-emulsion, and it often appears colored and 'milky.'

How to set up a reaction in water (e.g., cross-coupling reaction):

All solid reagents such as the catalyst, base, and coupling partners are weighed out and added to the reaction vessel containing the stir bar, then capped. The vessel is degassed by pulling vacuum and back-filling with an inert gas 3-5 times.*

Next, a degassed* surfactant solution (e.g., 2 wt % TPGS-750-M) is added, followed by any liquids (base or coupling partners) by syringe. The resulting solution is stirred vigorously at room temperature or heated by placing it in an oil bath. Reaction times range from minutes to 24 hours.

*If the reaction is not air-sensitive, degassing is not required.

Reaction monitoring:

Monitoring the reaction follows practices employed for typical organic transformations performed in organic solvents. A small aliquot can be removed with an argon- or nitrogen-flushed needle,* a disposable pipette, or TLC spotter through capillary action. The aliquot can be placed directly on a TLC plate. If the aliquot is monitored by GC or LC, filter the aliquot using EtOAc through a small disposal pipette containing 1-2 cm of silica gel to ensure removal of trace salts along with the surfactant.

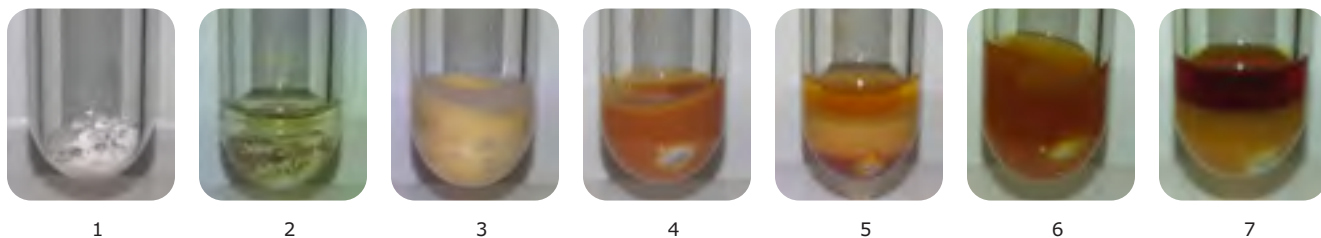
*Only if reagents/catalysts are air-sensitive.

Tips:

- Typically, most micellar reactions occur at 22-45 °C. If heating is required, the reaction vessel is removed from the oil bath and allowed to cool to room temperature before removing an aliquot.
- If the reaction mixture is highly viscous, removing an aliquot with a TLC spotter can be troublesome, so a disposable pipette is recommended instead.
- It is best to remove an aliquot from the reaction mixture while stirring in order to obtain an accurate level of conversion.

Reaction appearance:

Time lapse of a Suzuki–Miyaura cross-coupling reaction followed by an in-situ extraction of your product (see below).



1: reagents, 2: surfactant added, 3: after 1 minute, 4: reaction complete, 5: extraction solvent added, 6: extraction solvent mixing, 7: extracted product (top layer)

Reaction workup:

1) One-time use of the surfactant solution:

Upon reaction completion, EtOAc (typically) is added to the vessel. The entire mixture is then filtered through a plug of silica gel to remove the surfactant along with salt impurities. The crude mixture is then concentrated and purified by column chromatography.

2) In-situ extraction and recycling of the surfactant solution/catalyst:

After the reaction is complete, EtOAc (typically) is added to the vessel and mixed gently for ca. one minute at room temperature. Stirring is then halted, resulting in a biphasic mixture. Next, the top organic layer is extracted. This extraction process is performed 2-3 times. To reuse the surfactant solution, first full vacuum is pulled on the vessel to remove residual EtOAc. The vessel is then back-filled with an inert gas. The surfactant solution can be removed by syringe to be reused or additional catalyst,* base, and coupling partners can be directly added to the same vessel for the next reaction. The next reaction can be the same reaction with the same or different coupling partners, or a different reaction type.

*Additional catalyst might not have to be added if still catalytically active or if bound to the surfactant (e.g., PQS⁴⁻⁷).

Tip:

- During the extraction process, if the stirring rate is too high after the addition of organic solvent, phase separation can be problematic (i.e. difficult to see different phases or long separation times). To avoid this issue, decrease the stirring rate while mixing the extraction solvent, or use a centrifuge to aid phase separation.

3) Direct filtration:

After the reaction is complete, simply add water to crash out the product (product may already be precipitating), transfer it to a Büchner funnel while pulling vacuum, followed by washing the product with water, and drying. The product is then collected off the filter paper (Figure 3). This procedure has been shown to be feasible when the two coupling partners are in 1 to 1 stoichiometry. This direct filtration procedure has been demonstrated with Suzuki–Miyaura cross-couplings (particularly with aryl/heteroaryl-B(MIDA)⁸ and even 2-B(MIDA) pyridyl species⁹) in addition to other proprietary reactions developed at scale by Novartis.¹⁰ Utilizing this procedure allows complete avoidance of organic solvents during the reaction, the workup, and purification procedure. Although this filtration procedure avoids organic solvents during workup for reactions that are not performed at 1 to 1 stoichiometry, after the filtration procedure, additional purification will be necessary.

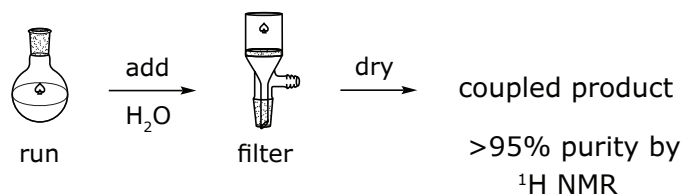


Figure 3. Direct filtration procedure using no organic solvents.

Where do I begin?

- add all reactants to your degassed vessel
- add 2 wt % surfactant/H₂O (under N₂/Ar)
- start with a 0.5 M concentration
- ensure vigorous stirring
- stir overnight at 22-45 °C

iv. Reaction setup (multi-gram scale)

Micellar catalysis is scalable, but a mechanical stirrer is often required to maintain vigorous stirring and thus high conversion. In this section, a Suzuki–Miyaura cross-coupling reaction performed at a 30 mmol scale is fully detailed. This representative procedure can be extended to additional micellar catalysis reactions.

Glassware used for representative example (vacuum filter-flask and separatory funnel omitted):



5-neck flask



5-neck flask



addition funnel



fritted-funnel

A detailed representative procedure for a Suzuki–Miyaura cross-coupling (> 5 g scale):

A 100 mL Ace European five-neck flask was equipped with the following: a 3 cm diameter glass stirring blade rod attached to a mechanical stirrer, a thermometer, an inlet line for nitrogen (or Ar), and a bubbler for a positive flow of inert gas. Under an inert atmosphere, the flask was charged with the aryl boronic acid (30 mmol, 1.0 equiv), heteroaryl chloride (30 mmol, 1.0 equiv), and $\text{PdCl}_2(\text{dtbpf})$ (147 mg, 0.225 mmol, 0.0075 equiv). The vessel was degassed with nitrogen for 10 min. Under a positive flow of an inert gas, a 2 wt % TPGS-750-M/ H_2O solution (60 mL) was added to the flask over 5 min by addition funnel, fitted to a side-arm while stirring at 400 rpm, after which the stirring rate was increased to 600 rpm. Under a positive flow of inert gas, triethylamine (12.7 mL, 90 mmol, 3.0 equiv) was added by addition funnel to the reaction mixture. After half of the base was added, the stirring was increased to 800 rpm. Upon completion of this addition, the stirring rate was decreased to 400 rpm. After 3 h of stirring at 25 °C, the reaction was complete (determined by LC-MS), and was transferred to a 250 mL separatory funnel* using EtOAc (100 mL). Another portion of EtOAc (50 mL) was added to fully dissolve the remaining solids. Two additional extractions were made with EtOAc (100 mL, then 50 mL). The organic phases were collected, and solvent was removed by rotary evaporation (40 °C, 170–160 torr). The crude material was then filtered through a porous glass funnel containing an activated charcoal/silica gel mixture and Cellflock 40. With 20% EtOAc/heptane (v:v, 100 mL, 3×) the solid was dissolved and transferred to the glass funnel and filtered under vacuum. The solvent was then removed by rotary evaporation (45 °C, 100–30 torr) resulting in a white solid that was dried in a vacuum oven for 24 h (45 °C, 25 torr) to afford the desired dried product (6.25 g, 94%) at 96% purity (determined by quantitative ^1H NMR spectroscopy).

*Although this example utilizes a separatory funnel for the workup, other options such as direct filtration, or performing the extraction in flask are amenable. The amount of organic solvent utilized for the workup was not optimized.

Time-lapse of a Suzuki–Miyaura reaction:



Reaction mixture before Et₃N
(not stirring)



Reaction mixture with Et₃N
(time = 0)
(stirring)



Reaction mixture at 3 h
(stirring)

Workup for Suzuki–Miyaura reaction:



extraction



fritted-funnel after filtration

Upon closer analysis of this chemistry at even larger scales, the CHAD department at Novartis noticed issues with their reaction mixtures not maintaining the required level of homogeneity as they scaled up—in addition to certain types of reactants/reagents being problematic at scale. To solve this issue, co-solvents were carefully picked and added to the reaction mixture (often, water-miscible solvents). When amenable, the same solvent utilized in the extraction process can be used as a co-solvent to avoid adding to the waste stream. Please refer to the following papers for further details about scaling up micellar catalysis reactions along with the role of co-solvents: (*Org. Lett.* **2017**, *19*, 194–197 and *Org. Process Res. Dev.* **2016**, *20*, 1388–1391).

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vi. General troubleshooting/optimization tips for micellar catalysis

Poor or inconsistent conversion. Stirring can often be the problem. Typically, reactions run in organic solvents are more forgiving with slower stirring rates if large exotherms are absent. These reactions are not homogeneous or heterogeneous, but somewhere in between. They are a micro-emulsion, therefore stirring is a very important parameter. Vigorous stirring is key but avoid splashing the reagents above the solvent level.

Increasing reaction rates. Empirically, adding salts (e.g., NaCl) to the surfactant solution can dramatically increase reaction rates. Through DLS measurements the salt additives increased the average size of the micelle, thus accommodating more reactants. Increasing the wt % of your surfactant or heating your reaction mixture is also recommended. Also, try using reagents that are more lipophilic; for example, conditions might require NaOt-Bu, but when switched to a 'greasy' base such as $i\text{Pr}_3\text{SiOK}$, a rate increase was observed, given its increased lipophilicity.

Screening surfactants. This is analogous to doing a solvent screen when optimizing a reaction in organic solvents. If the more commonly employed surfactants (TPGS-750-M or Nok) do not work, a quick screen through nonionic/ionic surfactants that are commercially available is recommended. Once a lead is found, most commercially available surfactants vary in their chain length (e.g., polyethylene glycol) and can be screened to see if this is a key reaction parameter. Lastly, always run a control reaction with just water. Usually the surfactant is necessary, but there are exceptions.

Organic bases vs. inorganic bases. While utilizing organic solvents, either an organic or inorganic base can be used, depending on your reaction. In micellar catalysis, organic bases typically work better (e.g., NMM, Et_3N). They aid in solubilizing troublesome crystalline material used in the reaction mixture, and can increase reaction rates.

Translating your reaction to micellar catalysis. One-for-one swapping of organic solvent to a surfactant mixture sometimes works, but getting a typical reaction to run under micellar catalysis often requires screening. In general, rules established in organic solvents do not translate to water.

Issues with phase separation during an in-situ extraction. Occasionally during an in-situ extraction procedure, phase separation is very poor. This can be fixed by gently stirring for approximately one minute after your extraction solvent is added. If separation is still poor, sonicate the vessel to break up the emulsion. If separation is still an issue, try extracting with different solvents.

Screening with transition metals and ligands. Many pre-catalysts and ligands are available commercially, but we found that common ones that were highly efficient in organic solvents can perform poorly in micellar catalysis. Given the extensive effort that has gone into developing organic reactions for organic solvents, rules have been established. This is not the case for water as the reaction medium has completely changed (in water = new rules). Start with catalysts and ligands (even bases) that have been previously published to work in water.

The reaction mixture is 'clumping' shortly after reaction setup. When dealing with insoluble reagents or highly crystalline materials, try increasing the wt % of the surfactant or heating your mixture first. Is it possible to switch either the base or acid to one that is liquid at room temperature? Can any of the reagents/additives be changed to increase lipophilicity? One trick is to add in water-miscible organic solvent (1–20%) to your reaction mixture. In some cases, water-immiscible solvent can be added, which can be the same solvent that is utilized during the extraction process (or in situ extraction process) to minimize solvent added to the waste stream.

Hydrolysis of your surfactant due to your base. Given the common ester functionality in many surfactants if highly basic or nucleophilic reagents are used, these could potentially hydrolyze the surfactant, although at the milder reaction temperatures used (22–45 °C), this is rare. Switching to a surfactant with less labile functional groups or reconsidering your base or strong nucleophile is recommended if the lipophilic portion of the amphiphile (i.e., vitamin E, phytosterols, etc.) is seen by TLC.

Reaction mixture is clumping at the end of the reaction. If reactions 'clump' near their point of completion, add solvent, briefly stir to dissolve the ball/clumps, and check the reaction by TLC, etc., before thinking that the reaction went awry. In most cases, this is your product crashing out. If your stoichiometry is 1 to 1 and minimal side-products are formed, this solid can be simply collected on a Büchner funnel, rinsing with water to remove salts, affording your desired product in good to high purity.

vii. Further reading and key reaction references

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