Reactivity of Styrenes in Micelles: Safe, Selective, and Sustainable Functionalization with Azides and Carboxylic Acids

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ABSTRACT: An amphiphile PS-750-M that mimics dipolar-aprotic organic solvents enables *N*-bromo succinimide (NBS)-mediated one-pot oxyfunctionalization of styrenes in water under mild conditions. Control experiments reveal the involvement of the radical pathway. The radical intermediate was also trapped with butylated hydroxytoluene to obtain peroxy educt. The method is scalable without involving any operational risk. This aqueous micellar technology for oxyfunctionalization is further applied on *in-situ* reduction and click chemistry to obtain *β*-azido alcohols and *β*-carbonyl triazoles.

KEYWORDS. micellar catalysis, chemistry in water, green chemistry, cross-couplings, styrene, azidation.

Introduction. Safe, sustainable, selective, and scalable (abbreviated as 4S) reaction methodologies are highly desirable.[1] In this regard, the word “safe” implies worker safety, environmental safety, process safety, and chemical safety.[2] As per the Organization for Economic Co-operation and Development, sustainable chemistry is a scientific concept that seeks to improve the efficiency with which natural resources are used to meet human needs for chemical products and services.[3] Therefore, efficiency, selectivity, and scalability of reactions heavily contribute towards a reaction’s sustainability. Along the same lines, green chemistry and sustainable chemistry are complementary.[4] The 12 Principles of Green Chemistry encourage use of safer solvents, along with providing many other ways of minimizing one’s environmental footprint.[2-5]

Besides its obvious natural abundance, water is usually considered among the safest of reaction solvents. It has been efficiently employed in “on water” and “in water” chemistry for many diverse transformations.[6-11] Aqueous micellar catalysis, a major enabler of chemistry in water, has recently gained attraction due to its applications to 4S reaction methodologies.[12-15] Many important transformations have been shown to occur in micellar media.[12-19] Our group has recently designed an amphiphile PS-750-M that structurally mimics the dipolar-aprotic solvent that enables several transformations which traditionally require DMF, DMAc, NMP, and 1,4-dioxane.[20-30] Additionally, the design hypothesis of PS-750-M assisted in gaining insight into how micellar nano-organometallic chemistry occurs. To date, preliminary answers to some fundamental questions are now in hand, such as, where and how chemistry occurs in micellar media, how reaction intermediates (radical,[23] carbene,[24] carbanion[25]) react under the shielding effect of micelles. To further advance micellar catalysis, an important question remains as to how micellar catalysis handles reactions involving substrates or intermediates which are generally unstable and traditionally require dipolar-aprotic solvents. From this standpoint, styrenes and azides are challenging due to their potential polymerization and unsafe decomposition, respectively.

Under the shielding effect of micelles, styrene and azide can be used safely, even when sequences involving radicals may be involved, as depicted in Figure 1, leading to useful educts *α*-azidoketones. Alternatively, other functional groups can be safely installed with this strategy. The *α*-functionalized ketone motifs, especially azidoketones and acyloxyketones, are valuable intermediates due to their broad synthetic utility to the pharmaceuticals, agrochemicals, and fine chemicals industries.[31-34] Therefore, various methods have been developed for their synthesis. The traditional approaches focus on either the substitution reaction of pre-functionalized starting materials or the oxidative coupling of carbonyl compounds in the presence of strong oxidants.[35-52] Among the most important synthetic methodologies for preparing azidoketones from alkenes involves $TMSN_3$-CrO_3 and CAN/NaN_3.[49,50] Likewise, oxidative coupling of alkenes and carboxylic acids to acyloxyketones has been reported using I_2/ TBHP catalytic system.[52] Recently, Reiser and co-workers have reported visible-light accelerated oxyazidation of styrene derivatives using [Cu(dap)$_2$Cl] as the catalyst.[53] However, all these reported methods have limitations, such as use of a metal catalyst,[53] and/or require excessive amounts of metallic or corrosive oxidants or toxic organic solvents.[51,52] Organic azides and peroxides are also known to be explosive, especially in flammable organic solvents,[54] further restricting their applications to large-scale reactions.

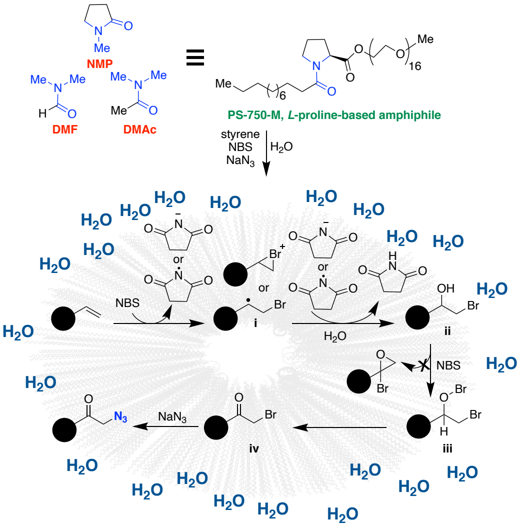
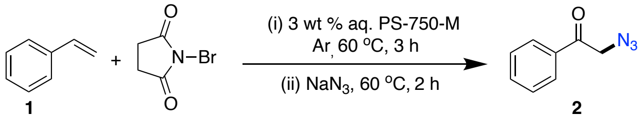


Figure 1. Mimicking the dipolar-aprotic solvents for oxyazidation of styrenes.

Based on these potential limitations and the importance of azidoketones and acyloxyketones, the application of micellar catalysis could lead to a catalyst-free, mild, safe, selective, sustainable oxyazidation and oxyacyloxylation, especially when the use of NBS in other oxyfunctionalization of styrenes is known.[55-58] We hypothesize that under the shielding effect of micelles, styrene can safely react with *N*-Bromosuccinimide (NBS) to generate bromonium ion or benzylic radical **i** (Figure 1), further reacting with a water molecule to generate **ii**. After reacting with NBS, the intermediate **ii** generates **iii** leading to **iv,** which subsequently reacts with an azide ion in one-pot generating desired *α*-azidoketone.

Table 1. Reaction optimization

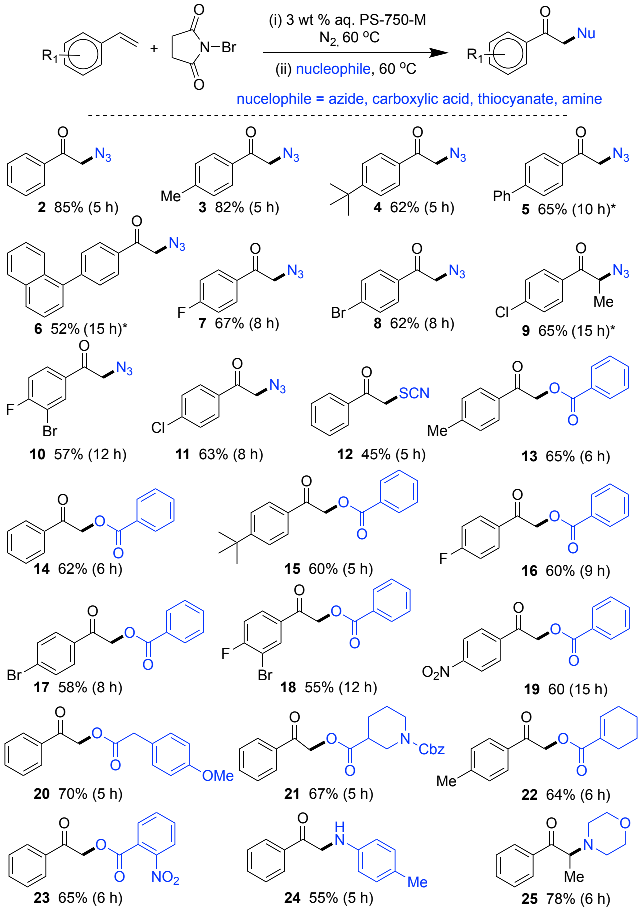


entry	deviation from standard conditions[a]	**2** (%)[b]
1	none	85
2	CH_3CN instead of PS-750-M	42
3	1,4-dioxane instead of PS-750-M	82
4	neat water instead of PS-750-M	65
5	NCS instead of NBS	traces
6	NIS instead of NBS	32
7	oxygen atmosphere instead of argon	22
8	20 mol % Bu_4NCl additive, 45 °C after azide addition[c]	69
9	20 mol % Bu_4NCl additive, rt after azide addition[c]	52

[a] Conditions: (i) 0.5 mmol **1**, 1.25 mmol *N*-Bromosuccinimide, 1 mL 3 wt % aq. PS-750-M, 60 °C, 3 h, argon atmosphere; (ii) 0.75 mmol sodium azide, 60 °C, 2 h, argon atmosphere. [b] Isolated yield. [c] Bromination step was performed at 60 °C for 3 h and azidation was performed using 20 mol % Bu_4NCl additive and 1.5 equiv NaN_3, 2 h.

Results and Discussion. We began our investigation with a standard reaction between styrene **1** and NBS, and subsequently reacting the resulting intermediate with NaN_3 in one-pot to obtain *α*-azidoketone **2** (for details, see Supporting Information). The reaction optimization involves dependence of reaction on several variables, such as, reaction temperature, global concentration, halogenating agent, and stoichiometry of reagents. A 60 °C reaction temperature, 0.5 M global concentration, NBS as a halogenating agent, 1:2.5 stoichiometry of styrene **1** and NBS, and 1.5 equiv NaN_3 were found to be the optimal (Table 1, entry 1). The reaction did not proceed efficiently when acetonitrile was used as a solvent instead of aqueous PS-750-M (entry 2). Notably, our amphiphile was designed to mimic the solvent polarity index of 1,4-dioxane, therefore, it was worth to compare the reactivity in PS-750-M versus1,4-dioxane. Although reaction was also clean in 1,4-dioxane, slightly less yield of **2** was obtained (entry 3). Reaction in neat water was not as effective as in aqueous PS-750-M (entry 4). The other halogenating agents, such as, NCS (*N*-chlorosuccinimide) and NIS (*N*-iodosuccinimide) were also not effective (entries 5, 6). Furthermore, reaction in the presence of ambient oxygen caused many unwanted byproducts and only 22 % conversion to the desired product was obtained (entry 7). These results indicates that the radical pathway is involved in the desired transformation. In optimal conditions, a slightly elevated temperature was required due to poor solubility of NaN_3 in micelles. The use of catalytic Bu_4NCl enables the azidation at 45 °C and rt (entries 8, 9). However, reaction rate was slower than the rate observed in optimized conditions.

Table 2. Substrate scope[a]

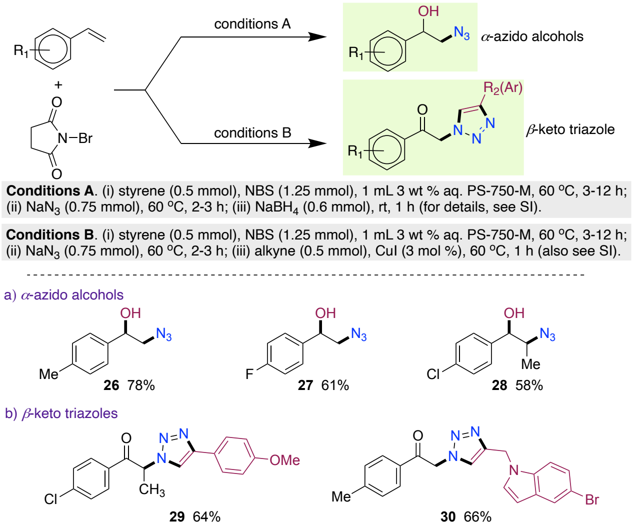


[a] Conditions: Styrene (0.5 mmol), NBS (1.25 mmol), nucleophile = NaN_3 (0.75 mmol) or carboxylic acid:K_2CO_3 (1:1, 0.75 mmol each) or amine (0.75 mmol) or KSCN (0.75 mmol), 1 mL 3 wt % aq. PS-750-M, 60 °C, argon atmosphere, overall reaction time is given for all examples. *Reactions were carried out using 3 equiv NBS (for details, see SI).

Next, this technology's scope was examined on a wide range of substrates including the different nucleophiles other than azide (Table 2). The nucleophiles include azide (**2-11**), thiocyanate (**12**), carboxylic acids (**13-23**), and amines (**24**, **25**). Oxyazidation was tolerable to electron-rich (**3**, **4**) as well as electron-deficient styrenes (**7-11**). Functional groups, such as, fluoro (**7**, **10**), bromo (**8**, **10**), chloro (**9**), and nitro (**19**) were well tolerated. Notably, good yield was obtained in the styrene substrate containing nitro group (**19**), and no side reaction with the nitro group was observed. A good yield was also obtained with internal olefin (**9**). Although acids are weak nucleophiles compared to azide, a decent reactivity was observed with aromatic and non-aromatic acids (**13-23**). Electron-rich (**13**, **15**) and electron-deficient (**16-19**) styrenes displayed good-to-excellent reactivity with carboxylic acid nucleophiles. Likewise, both the electron-rich (**20**, **21**) and electron-deficient (**23**) acids showed suitable reactivity. Notably, acid possessing alkyl amine residue (**21**) and reactive allylic carbon (**22**) displayed good reactivity and selectivity. No side reaction at the *N*-Cbz and cyclohexene residues was observed in examples **21** and **22**, respectively. Reactivity of *p*-toludine and morpholine with styrene was also good as illustrated in example **24** and **25**.

The versatility of this aqueous technology was further explored for one-pot carbonyl reductions and copper-catalyzed 1,3-dipolar cycloaddition between resulting azides and alkynes (Table 3).[59,60] In other words, without isolation of *α*-azidoketones, carbonyl reduction and cycloaddition reactions were performed in a same pot. For carbonyl reductions, azide remained intact upon reaction with $NaBH_4$ (**26**-**28**). Likewise, after initial oxyazidation, an addition of 3 mol % CuI as a catalyst and 1.0 equivalent alkyne in a same pot affords triazole educts **29** and **30** in good yields.

Table 3. One-pot carbonyl reduction and 1,3-dipolar azide-alkyne cycloaddition reactions[a]



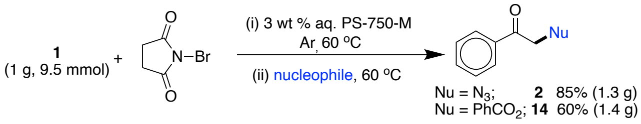
Conditions A. (i) styrene (0.5 mmol), NBS (1.25 mmol), 1 mL 3 wt % aq. PS-750-M, 60 °C, 3-12 h; (ii) NaN_3 (0.75 mmol), 60 °C, 2-3 h; (iii) $NaBH_4$ (0.6 mmol), rt, 1 h (for details, see SI).

Conditions B. (i) styrene (0.5 mmol), NBS (1.25 mmol), 1 mL 3 wt % aq. PS-750-M, 60 °C, 3-12 h; (ii) NaN_3 (0.75 mmol), 60 °C, 2-3 h; (iii) alkyne (0.5 mmol), CuI (3 mol %), 60 °C, 1 h (also see SI).

[a]All yields are isolated.

Next, the technology's robustness was further explored on gram scale reactions using styrene **1** and azide or carboxylic acid nucleophiles (Scheme 1). The isolated yields of **2** and **14** in gram-scale reactions were comparable with the ones performed on 0.5 mmol scale (see Table 2).

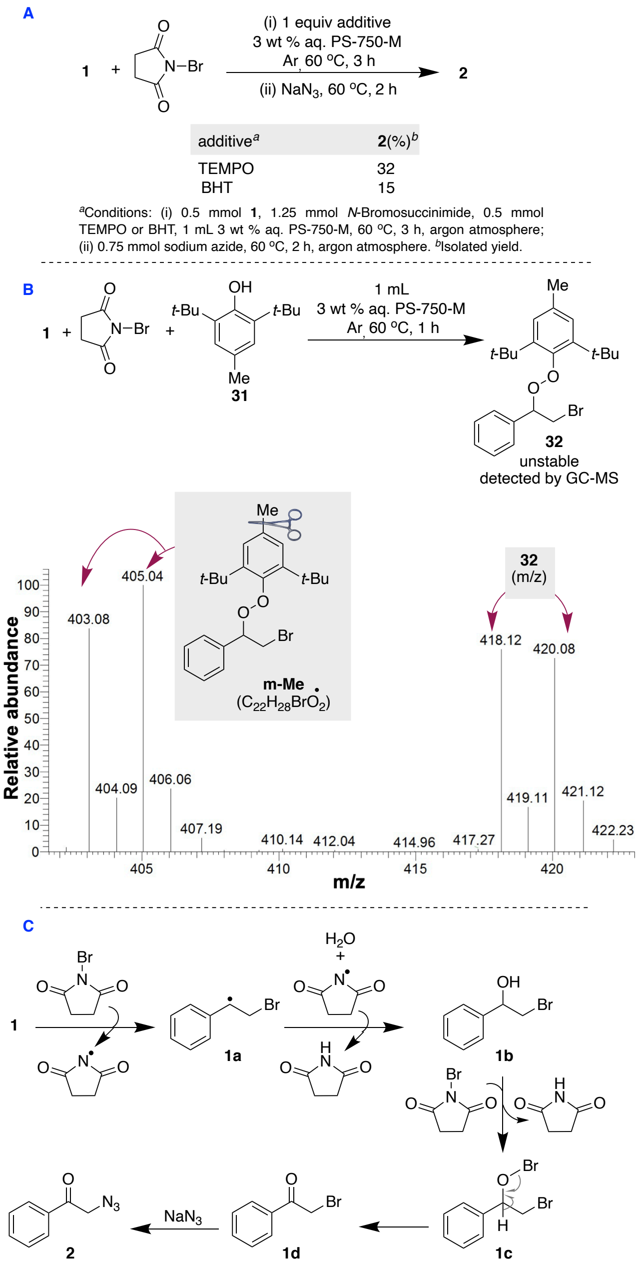
Scheme 1. Gram scale reactions[a]



Conditions: **1** (9.5 mmol), NBS (23.8 mmol), 19 mL 3 wt % aq. PS-750-M, 60 °C for 4 h then addition of NaN_3 (14.25 mmol) or $PhCO_2H$: K_2CO_3 (1:1, 14.25 mmol each), 60 °C for additional 2 h (for details, see SI).

Next, control experiments were performed to confirm whether the reaction pathway involves radical intermediates or not. An oxyazidation reaction of **1** in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) radical or BHT (butylated hydroxytoluene) inhibits the reaction, indicating involvement of radical in the reaction pathway. Only 32% and 15% desired product was obtained in the presence of TEMPO and BHT, respectively (Scheme 2A). Most likely, a radical intermediate is involved before the reaction with azide nucleophile. For confirmation, a reaction of **1** with NBS in the presence of BHT were attempted in micellar medium without the use of NaN_3 (Scheme 2B). A GC-MS analysis of the reaction mixture indicated the trapping of resulting radical with **31** (BHT) and formation of peroxide **32**. An attempt to isolate the pure intermediate **32** was unsuccessful due to its instability. In GC-MS spectrum, signals at *m/z* 418 and 420 in 1:1 intensity ratio confirmed the presence of bromo functional group. The presence of m-Me signal at *m/z* 403 and 405 further supported the trapping of radical.

Scheme 2. (A) Control experiments with TEMPO and BHT; (B) Radical Trapping; (C) Plausible reaction pathway



additive[a]	2(%)[b]
TEMPO	32
BHT	15

[a]Conditions: (i) 0.5 mmol **1**, 1.25 mmol *N*-Bromosuccinimide, 0.5 mmol TEMPO or BHT, 1 mL 3 wt % aq. PS-750-M, 60 °C, 3 h, argon atmosphere; (ii) 0.75 mmol sodium azide, 60 °C, 2 h, argon atmosphere. [b]Isolated yield.

Based on control experiments (*vide supra*), a plausible reaction pathway is described in Scheme 2C. A reaction of styrene

1 with NBS generates stable radical **1a**. The hydrogen atom transfer radical abstraction from water by succinimide radical likely results in formation of *α*-hydroxy bromide **1b**. A hydrogen atom exchange between NBS and **1b** further forms **1c**, which most likely immediately converts to **1d**. This event generates 1.0 equivalent HBr. An addition of sodium azide to the reaction mixture cause slow formation of hydrazoic acid which causes nucleophilic substitution in **1d** and forms product **2**. The HBr generation after reaction completion is evidenced by drop of pH from 3.28 to 1.68.

Conclusions. In summary, with the use of aqueous micelles of proline-derived PS-750-M, azidoketones and acyloxyketones can be accessed in a safe way. The synthetic protocol meets the safety standard. The *in-situ* generation of hydrazoic acid and its anticipated greater solubility in micellar medium enables oxyazidation of styrene. Likewise, safe oxyamination of styrenes is also possible with the same approach. More similar reports on trifluoromethylation will be published in a due course.

ASSOCIATED CONTENT

Supporting Information

Materials and Methods, Detailed Optimization Studies, General Reaction Procedure, Supplementary Figures, Supplementary Tables, Supplementary Schemes, Analytical Data, ^{1}H and ^{13}C NMRs (PDF).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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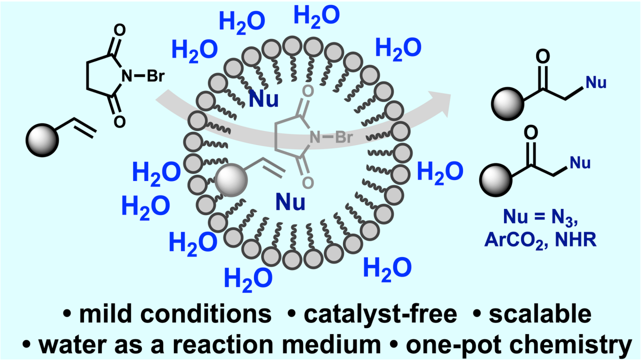

The shielding effect of micelles of commercially available PS-750-M enables sustainable and safe oxy-functionalization (including azidation) in water.