RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

JournalName

ARTICLE

Efficient Passerini reactions in an aqueous vesicle system

Daniel Paprocki,[a] Dominik Koszelewski,[a] Peter Walde*[b] and Ryszard Ostaszewski*[a]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

As an example of a one-pot multicomponent reaction, the formation of α-acyloxy carboxamides from a carboxylic acid, an aldehyde and an isocyanide (Passerini reaction) was investigated in aqueous solution in the presence of different types of surfactants. With dioctadecyldimethylammonium bromide (DODAB), a known vesicle-forming cationic surfactant, the reaction with hydrophobic starting materials proceeded with higher yields than without DODAB and with higher yields than in dichloromethane. These results demonstrate the potential of aqueous surfactant vesicle systems as promoters of multicomponent reactions.

Introduction

The use of water as a solvent for organic transformations offers several environmental benefits. Therefore, water as a reaction medium has received considerable attention in synthetic organic chemistry, since it is an inexpensive, non-toxic and non-flammable solvent.[1] The use of water as a medium for organic reactions provides properties which may be advantageous for many reactions.[2] However, one major disadvantage in the use of water as a solvent for the synthesis or transformation of organic compounds is that most organic molecules are insoluble in water. To circumvent this disadvantage, surfactants (amphiphiles), which can solubilize organic molecules, have been employed. The presence of surfactants not only ensures higher solubility of hydrophobic compounds in water but may also enhance reaction rates.[3] This rate-enhancing effect can be explained by at least three effects: the increased concentration of the reacting species in the area of the aggregates formed from the surfactants (*e.g.*, micelles, vesicles), a different polarity of the actual locus where the reaction takes place, and possible steric hindrance so that the extent of side reactions is decreased.[4] Meanwhile, the use of aqueous surfactant systems instead of organic solvents gains importance from the view point of green chemistry.[5]

Certain amphiphiles, like decanoic acid, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC), sodium bis (2-ethylhexyl) sulfosuccinate (AOT) and dioctadecyldimethylammonium bromide (DODAB), form bilayer structures in aqueous media (dispersed artificial vesicles). Such vesicles have been used at room temperature for a variety of chemical reactions as reaction promoters.[4] Furthermore, artificial vesicles are also prepared and investigated as models of protocells and for the construction of artificial cell-like systems,[6] or for vaccination.[7] Vesicles are well-known for their use – or potential use – as drug delivery systems, since hydrophilic and/or lipophilic drugs can be hosted by vesicles.[8]

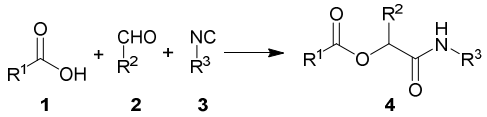
With respect to literature data on the promotion (acceleration) of chemical reactions in the presence of bilayer- (vesicle-) forming surfactants, several examples are known.[4] For example, the unimolecular decarboxylation of 6-nitrobenzisoxazole-3-carboxylate is accelerated in the presence of vesicles containing cationic surfactants (*e.g.*, DODAB), more efficiently than in the presence of micelle-forming hexadecyltrimethylammonium bromide.[9] Other examples are a Cu^{2+} catalyzed Diels-Alder reaction[10] or an amino-acid catalyzed synthesis of tryptophan.[11] There are also a few reports about enantioselective reactions promoted by vesicle containing membrane-embedded chiral peptides.[12]

We were wondering whether artificial vesicles can also be used for the promotion of *multicomponent reactions* (MCRs). Recently, several MCRs were already carried out in micellar systems. For example, the Mannich reaction,[13] the Kinugasa reaction,[14] the Betti bases synthesis,[15] the preparation of chromeno[2,3-*b*]quinolinedione derivatives,[16] or the synthesis of 2-aminobenzothiazolomethyl naphthols.[17] MCRs enable to synthesize new compounds from three or more reactants, where basically all or most of the atoms of the reactants contribute to the newly formed product.[18] The classic reaction between carboxylic acids, carbonyl compounds (aldehydes or ketones) and isocyanides, described by Passerini in 1921 and later given his name, provides α-acyloxy carboxamides in a one step procedure (Scheme 1). This is the first example of a family of reactions called isocyanide-based MCRs (abbreviated as I-MCRs).

The Passerini reaction is interesting because it has 100% atom-economy. This means that every atom in the starting materials is incorporated in the product. Consequently, there is no

[a] *Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*
[b] *Laboratory of Polymer Chemistry, Department of Materials, ETH Zurich, Vladimir-Prelog-Weg 5, 8093 Zurich, Switzerland*
† *Footnotes relating to the title and/or authors should appear here.*
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

intrinsic chemical waste associated with the reaction. MCRs, like the Passerini reaction, have been used extensively in the field of combinatorial chemistry.[18] Applying 10 different isocyanides, 10 different carboxylic acids and 10 different aldehydes leads readily to hundreds of different compounds.



Scheme 1 The Passerini reaction. A carboxylic acid (**1**), an aldehyde (**2**) and an isocyanide (**3**) react to form an α-acyloxy carboxamide (**4**).

The P-MCR is usually performed in aprotic organic solvents such as dichloromethane or toluene, which are toxic and carcinogenic.[19] However, Pirrung, Das Sarma and others have shown that the P-MCR can be performed efficiently in water.[20] Due to the mentioned benefits of MCRs, their combination with aqueous media constitutes one of the highlighted subclasses of *ideal synthesis*. Indeed In recent years, green chemistry has drawn the attention of synthetic chemists also for MCRs.[21] It is evident that the possibility of using water as green solvent for organic multicomponent reactions is in the spotlight of many research groups.

The use of micelle- and vesicle-forming surfactants in aqueous solutions can be viewed as a convenient alternative for performing Passerini multicomponent reactions in the absence of organic solvents. This is interesting not only from a purely scientific point of view, but also with respect to possible applications. The common P-MCR products, α-acyloxy carboxamides and α-hydroxy carboxamides, are key building blocks for the synthesis of natural products and drugs. These compounds are used for the synthesis of γ-lactones,[22] 2-furanones,[23] peptides,[24] peptidomimetics,[25] and both enantiomers of α-amino acids.[26]

The research interest of our group is the application of enzymes and microorganisms in organic synthesis[27] and the application of MCRs and enzymatic procedures for the synthesis of chiral peptidomimetics.[25,28] Moreover we investigated a first enzyme-catalyzed Ugi-MCR.[29] Performing Passerini reactions in the presence of vesicle systems – which are expected to be less deleterious to enzymes than micellar solutions – may be a suitable way for combining MCRs with enzymatic procedures.[30] Entrapping enzymes inside artificial vesicles – or binding enzymes to vesicles – may enable (i) the one-pot synthesis of α-acyloxy carboxamides, followed by enzymatic hydrolysis to yield optically enriched α-hydroxy carboxamides, or (ii) the preceding preparation of starting materials by enzyme-catalyzed reactions within the same pot for a MCR, *e.g.,* the enzymatic oxidation of an alcohol, followed by the Passerini reaction. This subject is part of further studies.

Results and discussion

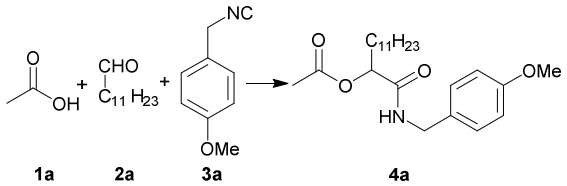
For the first set of experiments, we have chosen as model reaction of the P-MCR the reaction of acetic acid (**1a)**, dodecyl aldehyde (**2a)** and *p*-methoxybenzylisocyanide (**3a)**. In order to compare results in micellar/vesicular systems with those obtained under standard conditions (organic solvents), we studied the influence of different solvents on the reaction course. The results are shown in Table 1. Dichloromethane was the best among the tested solvents, although the reaction takes place in all the solvents used. In diethyl ether, in alcohols, ethyl acetate and in acetonitrile, the yields were poor. Yields obtained in distilled water or in aqueous phosphate buffer saline (PBS) were about half the yield in dichloromethane.

We then focused our work on aqueous reaction systems and investigated the effect of surfactants on the model Passerini reaction – using **1a**, **2a**, and **3a** – in PBS, without the use of any organic solvent. The main drawback in using aqueous solutions is the low solubility of most organic substances in water, which could be overcome by addition of surfactants. We tested the effect of adding well-known micelle-forming (*e.g.* SDS) as well as vesicle-forming surfactants to PBS. Vesicle-forming surfactants (*e.g.* DODAB) are of special interests due to their potential usefulness for a combination of the (chemical) P-MCR with enzyme-catalyzed transformations (see above).

The surfactants were added at 20 mol%, which refers to the concentration of the individual starting materials. For comparison, the effect of a few other additives was also tested. The yields obtained are summarized in Table 2.

In the presence of inorganic salts (entries 2-4), the yields were the same or slightly lower than without salt. In the presence of Montmorillonite K 10 (entry 5) the yield was also lower than in PBS alone. Entries 6 and 7 show, that addition of anionic surfactants hinders the reaction to take place, probably due to repulsive interactions between the acetate ions (deprotonated form of **1a**) and the negatively charged surface of the micellar or vesicular aggregates formed. Addition of cholesterol (entry 8) also decreases the reaction yield. The presence of non-ionic surfactants has a favorable effect (entries 9-11): The reaction yields for the model P-MCR were between 43 and 47 %, significantly higher than in PBS (33 %). The best results, however, were obtained in the presence of cationic surfactants (entries 12-13), particularly DODAB (entry 14). This amphiphile is known to form bilayers in aqueous solutions, present as dispersed vesicles.[4,31] The positive effect of cationic surfactants like DODAB on the Passerini reaction is probably due to two main effects, (i) an increase of the solubility of the reacting molecules in the hydrophobic part of the bilayered vesicular aggregates and (ii) electrostatic attractions between the cationic surface of the vesicles and the acetate ions. This leads to increased local concentrations of the reacting molecules in the region of the vesicle bilayers and therefore to a promotion of the reaction. Comparing of entries 3, 13 and 14 proofs that the accelerating effect is due to the presence of cationic DODAB, and not due to the bromide anion.

Table 1 Effect of different solvents on the model Passerini reaction[a]



1a **2a** **3a** **4a**

Entry	Solvents	Yield[b] (%)
1	Dichloromethane	59
2	Diethyl ether	31
3	Acetonitrile	21
4	Ethanol	16
5	Ethyl acetate	13
6	Methanol	10
7	TBME	10
8	Distilled water	32
9	PBS (pH 7.4)	33

[a] Reaction conditions: acetic acid (**1a,** 0.1 mmol), dodecyl aldehyde (**2a,** 0.1 mmol) and *p*-methoxybenzylisocyanide (**3a**, 0.1 mmol) in solvent (1 mL) for 24 h at 20 °C.
[b] Isolated yields of **4a**.

For gaining more insight into the effect of DODAB on the model Passerini reaction, the reaction was studied by varying the DODAB concentration, ranging from 1 to 100 mol%. All DODAB concentrations which were above critical micelle concentration (for H_2O, 25°C, $4.28*10^{-5}$ M). [32] The reaction yields were determined by HPLC. The results are shown in Fig. 1. In all cases, the yields were higher than in PBS. While upon increasing DODAB from 1 to 20 mol%, the yield of the target product **4a** increased up to 58%, further increase from 20 to 100 mol%, did not increase the yield more. Based on these data, DODAB as vesicular additive was used at a concentration of 20 mol % for all further measurements as optimal concentration.

From an environmental point of view, the reusability of the surfactant used is a critical issue. Therefore, we investigated whether the DODAB vesicular suspension can be used more than once. Again, the model Passerini reaction was carried out with **1a**, **2a** and **3a** for 24 h at room temperature in the presence of 20 mol% DODAB. During the progress of the reaction, crystals of product **4a** are forming and falling out from the reaction mixture. The crystals could be separated by filtration through wadding (filter papers and frits led to plugging by the surfactant). The filtrate containing DODAB was then used for a next reaction run. The precipitate of **4a** was washed with water and purified by recrystallization from hexane/ethyl acetate or analyzed by HPLC. The results from these DODAB reusability tests are shown in Fig. 2. DODAB could be reused three times without appreciable decrease in yield. Afterwards, there was a drop in yield from about 50-55 % to about 35 %, almost the same value as obtained in PBS without additive.

.

Table 2 Effect of different additives on the model Passerini reaction in PBS[a].

Entry	Additive (0.02 mmol)	Yield[b] (%)
1	---------	33
2	$CaCl_2$	25
3	NaBr	29
4	NaCl	33
5	Montmorillonite K 10 (10 mg)	24
6	Sodium dodecyl sulphate (SDS)	1
7	Sodium bis(2-ethylhexyl) sulfosuccinate (AOT)	2
8	Cholesterol	20
9	Span 60	43
10	Tween 80	46
11	Triton X-100	47
12	Didodecyldimethylammonium bromide	48
13	Dioctadecyldimethylammonium bromide (DODAB)	58
14	DODAB (0.02 mmol) + NaCl (0.02 mmol)	55

[a] Reactions (1 mL) were carried out with acetic acid (**1a**, 0.1 mmol), dodecyl aldehyde (**2a**, 0.1 mmol) and *p*-methoxybenzylisocyanide (**3a**, 0.1 mmol) for 24 h at room temperature.
[b] Yields of **4a** determined by HPLC analysis.

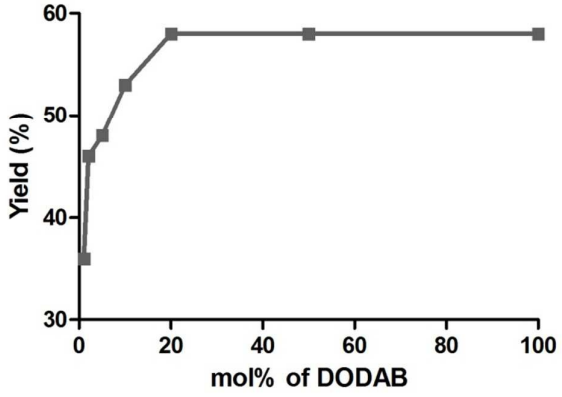


Fig. 1 Effect of mol% of DODAB on the isolated yield of **4a** of the model Passerini reaction. Reaction conditions: acetic acid (**1a,** 0.1 mmol), dodecyl aldehyde (**2a,** 0.1 mmol) and *p*-methoxybenzylisocyanide (**3a**, 0.1 mmol) in 1 mL PBS for 24 h at 20 °C.

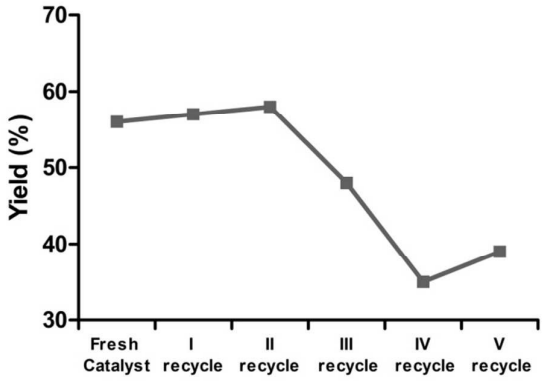
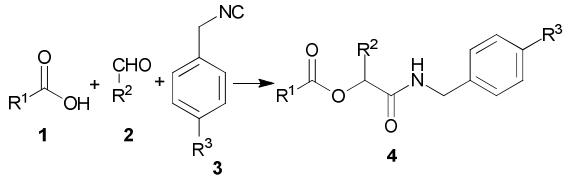


Fig. 2 Reusability of DODAB as determined through the isolated yield of **4a** for the model Passerini reaction. Reaction conditions: acetic acid (**1a,** 0.1 mmol), dodecyl aldehyde (**2a,** 0.1 mmol) and *p*-methoxybenzyl isocyanide (**3a**, 0.1 mmol) in 1 mL PBS for 24 h at 20 °C.

After optimization of the reaction conditions for the model Passerini reaction, the reaction was also carried out with other carboxylic acids, aldehydes and isocyanides to afford the corresponding α-acyloxy carboxamides. The isolated yields were determined after 24 h at room temperature, and comparison was made with the same reactions carried out in dichloromethane. The results are summarized in Table 3. They show that the reactions carried out with acetic acid (**1a**), *p*-methoxybenzylisocyanide (**3a**) and a hydrophobic aldehyde with a long alkyl chain (dodecanal (**2a**) or nonanal (**2b**)) gave comparable yields in the presence of DODAB and in dichloromethane (entries 1+3). Replacing **3a** with benzylisocyanide (**3b**) results in a higher yield in the presence of DODAB, while the same or slightly better yields are obtained in dichloromethane (entries 2 and 4). Similar reactions with aryl instead of alkyl aldehydes gave lower yields (entries 5-7), and the yields obtained in dichloromethane are higher than in the aqueous DODAB system. Reactions carried out with the more hydrophobic benzoic acid (**1b**) instead of acetic acid (**1a**) resulted in higher yields (entries 8-15).

Benzoic acid (**1b**), dodecanal (**2a**) and *p*-methoxybenzylisocyanide (**3a**) stirred in water in the presence of DODAB gave product **4h** with 94 % yield, besides 68 % in dichloromethane (entry 8). Reactions of **1b** and **2a** or **2b** with benzylisocyanide (**3b**) in the DODAB system resulted in lower yields as compared to those with **3a** (entries 8-13). It is the opposite effect as in the reactions with acetic acid (**1a**). It may be due to odds in polarity and solubility of acids in water. Aryl aldehydes (**2c** and **2d**) gave only slightly lower yields than hydrophobic alkyl aldehydes (**2a** and **2b**), but still higher ones if compared to the same reaction carried out in dichloromethane.

Table 3 Comparison of Passerini reactions carried out in an aqueous DODAB system and in dichloromethane.



1a: $R^1=CH_3$ **2a**: $R^2=C_{11}H_{23}$ **3a**: $R^3=OMe$
1b: $R^1=C_6H_5$ **2b**: $R^2=C_8H_{17}$ **3b**: $R^3=H$
1c: $R^1=C_2H_5(CH_3)CH$ **2c**: $R^2=C_6H_5$
2d: $R^2=p\text{-}NO_2C_6H_4$

Entry	1	2	3	4	Yield[a] (%)	Yield[b](%)
1	**1a**	**2a**	**3a**	**4a**	58	59
2	**1a**	**2a**	**3b**	**4b**	67	58
3	**1a**	**2b**	**3a**	**4c**	47	51
4	**1a**	**2b**	**3b**	**4d**	78	62
5	**1a**	**2c**	**3a**	**4e**	19	40
6	**1a**	**2d**	**3a**	**4f**	17	32
7	**1a**	**2d**	**3b**	**4g**	26	31
8	**1b**	**2a**	**3a**	**4h**	94	68
9	**1b**	**2a**	**3b**	**4i**	91	75
10	**1b**	**2b**	**3a**	**4j**	80	69
11	**1b**	**2b**	**3b**	**4k**	77	64
12	**1b**	**2c**	**3a**	**4l**	92	73
13	**1b**	**2c**	**3b**	**4m**	82	64
14	**1b**	**2d**	**3a**	**4n**	74	58
15	**1b**	**2d**	**3b**	**4o**	72	48
16	**1c**	**2a**	**3a**	**4p**	64[c]	55[c]

[a] Reactions were carried out with carboxylic acid (0.5 mmol), aldehyde (0.5 mmol) and isocyanide (0.5 mmol) in PBS (5 mL) for 24 h at room temperature, using DODAB (0.1 mmol) as additive.

[b] Reactions were carried out with carboxylic acid (0.5 mmol), aldehyde (0.5 mmol) and isocyanide (0.5 mmol) in dichloromethane (5 mL) for 24 h at room temperature.

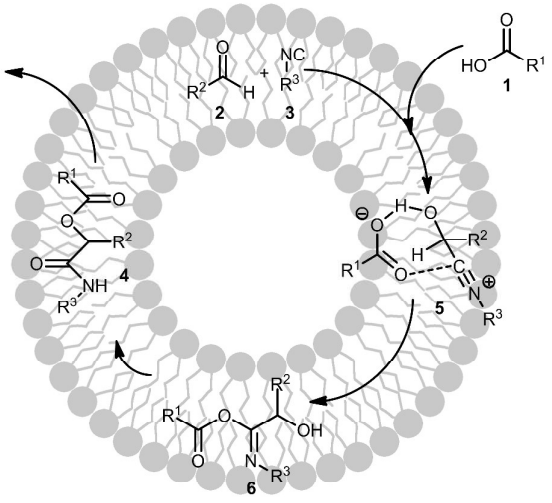
[c] Mixture of diastereoisomers, dr = 1:1, determined by ^{1}H NMR.

To investigate the possible influence of DODAB on the diastereoselectivity of the Passerini reaction, we preformed the reaction shown in entry 16 with racemic 2-methylpropionic acid (**1c**), dodecanal (**2a**) and *p*-methoxybenzylisocyanide (**3a**). Both in dichloromethane and in water, the diastereomeric ratio was 1:1, which means that in this case the (achiral) DODAB vesicles do not influence the diastereoselectivity of the reaction, which is a reasonable finding. The yield of product **4p** obtained in the DODAB system was slightly higher (64 % compared to 55 % in dichloromethane).

The product with the highest yield (94 %) was obtained in the reaction of benzoic acid (**1b**), dodecanal (**2a**) and *p*-methoxybenzylisocyanide (**3a**) (entry 8 in Table 3). In a control measurement we performed this reaction in water and PBS without DODAB. In water, the yield was 70 %, in PBS 58 %, which indicates that the DODAB vesicle system acts as promoter of the Passerini reaction. Moreover, we have carried out the same reaction in water under the published

conditions,[20] which means with 40 mM substrates (instead of 100 mM). Product **4h** was obtained with 67 % yield. This undoubtedly demonstrates the benefits of the aqueous vesicle system.

The aldehydes and isocyanides used in this work are hydrophobic molecules. They are expected to migrate into the hydrophobic vesicle membrane. Moreover the carboxylic anion is attracted by the positively charged surface of the DODAB vesicles. Inside the membrane of the vesicles, the Passerini reaction is assumed to take place according to the widely accepted mechanism,[33] including presence of nitrilium ion intermediate, postulated by DFT calculations[34] (Scheme 2). The reaction occurs more easily, than in water due to the presence of vesicles non-polar membrane,[1,3] in contrast to the reaction in a protic solvent, where hydrogen bonds are responsible of the increasing barrier of the rate-determining step.[34] Firstly reaction of aldehyde **2**, carboxylic acid **1** and isocyanide **3** leads to nitrilium–carboxylate ion-pair **5**. This ion pair in the absence of hydrogen bond with water decreases reactants reactivity what enhances reaction yields. The next step is the C–O bond formation, which results in intermediate **6** formation. The final product **4** arises from a rearrangement of intermediate **6** (Scheme 2). Afterwards solid products **4** are expelled from the vesicle membrane and precipitate from solution. This product precipitation certainly helps shifting the reaction towards the products.[35]



Scheme 2 Schematic representation of a plausible mechanism for the Passerini reaction[18,33,34] occuring in the DODAB vesicle system. Note that the vesicle size and membrane diameter are not drawn to scale. Without mechanical treatment, such as sonication or polycarbonate membrane extrusion, DODAB in aqueous solution forms heterogeneous micrometer-sized multilamellar vesicles.

Conclusions

During our studies, we have investigated the influence of different aqueous surfactant systems on the Passerini multicomponent reaction. Based on the results obtained, we have developed a new, green protocol. This protocol allows to synthesize α-acyloxy carboxamides in aqueous solution in the presence of the vesicle-forming surfactant DODAB at room temperature. Application of DODAB substantially improves the preparation of the Passerini reaction products in aqueous solution, in general providing corresponding α-acyloxy carboxamides with higher yields as compared to those obtained under standard conditions in dichloromethane or water. Moreover, due to the higher concentration of substrates (100 mM) compared to the protocol conducted in water (40 mM),[20] the productivity in the presence of the vesicles is significantly higher than in the absence of the vesicles. The vesicle membranes act as reaction promoters in the sense that they host the reaction for efficient intermolecular couplings to take place. Moreover, the reusability of the vesicle system was investigated. Our results clearly indicated that instead of dichloromethane water micellar system can be reused, which fulfills one of the green chemistry principles and is of great importance for future applications. The simple work up procedure, the minimal usage of organic solvents (only for further purification) and the good to excellent reaction yields fulfill the requirements for an environmentally friendly process. This protocol provides mild conditions which may be compatible with enzymatic catalysis which will be explored in our future work. The work carried out so far, and reported in this paper, is the first attempt to synthesize α-acyloxy carboxamides using surfactants in aqueous systems at room temperature.

Acknowledgements

We gratefully acknowledge the financial support of NCN project Harmonia No 2014/14/M/ST5/00030 for financial assistance. This work is the outcome of ideas discussed at a Systems Chemistry meeting of the COST action CM1304.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded with Varian 200 MHz and Bruker 400 MHz spectrometers, with TMS used as an internal standard or the residual chloroform signal. HPLC analysis were performed with a ProStar HPLC instrument (Varian/Agilent Technologies) equipped with a Kromasil C18 column (5 µm; 250×4 mm; flow rate 1 mL/min; eluent: acetonitrile/water (70:30, v/v), λ=254 nm. CHN analysis was performed on a Vario EL III (Elementor) elemental analyzer. High resolution mass spectrometry (HR:MS) spectra were recorded on an Mariner (PerSeptiveBiosystems) and Synapt G2:SHD apparatus. Melting points were determined with a model SMP-20 device (Büchi, Flawil, Swizerland). Phosphate buffer saline (PBS) was prepared from PBS tablets bought from Sigma Aldrich, yielding 0.01 M phosphate buffer, 0.0027 M potassium chloride and 0.137 M sodium chloride, pH 7.4 at 25

°C. Dioctadecaldimethylammonium bromide (DODAB), purity ≥98.0 % (AT), was purchased from Sigma Aldrich, product number 40165. Dilauryldimethylammonium bromide (= didodecyldimethylammonium bromide, purity >98.0 %), was purchased from TCI, product number D1974. Dioctyl sulfosuccinate sodium salt (AOT = sodium bis (2-ethylhexyl) sulfosuccinate, purity 98 %), was purchased from Sigma Aldrich, product number 323586. Sodium dodecyl sulfate (SDS), purity ≥99.0 % (GC), was purchased from Sigma Aldrich, product number L6026. Cholesterol, purity ≥99.0 %, was purchased from Sigma Aldrich, product number C3045. Triton X-100, was purchased from Sigma Aldrich, product number T9284. Sorbitan Monostearate (Span 60), was purchased from TCI, product number GL01-YQ. Tween 80, was purchased from Schuchardt München (now Merck). *p*-Methoxybenzylisocyanide (**3a**) was synthetized from *p*-mehoxybenzylamine in two-step synthesis (see Supporting Information). The remaining starting materials for the Passerini reaction were purchased from Sigma Aldrich or TCI.

General procedure A for the synthesis of compounds 4a-p. A mixture of aldehyde (0.5 mmol), carboxylic acid (0.5 mmol) and isocyanide (0.5 mmol) was stirred at room temperature in PBS (5 mL) in the presence of DODAB (0.1 mmol). After 24 h the reaction mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried with $MgSO_4$ and residuals of solvent were removed by distillation under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/AcOEt as eluent. NMR spectra are given in Supporting Information.

General procedure B for the synthesis of compounds 4a-p. A mixture of aldehyde (0.5 mmol), carboxylic acid (0.5 mmol) and isocyanide (0.5 mmol) was stirred at room temperature in dichloromethane (5 mL). After 24 h the solvent was distilled under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/AcOEt as eluent.

Reusability of surfactant. In the case of the general procedure A, the aqueous filtrate containing surfactant was reused with a mixture of acetic acid (1 mmol), dodecyl aldehyde (1 mmol) and *p*-methoxybenzylisocyanide (1 mmol) for 24 h at room temperature.

Procedure for analytical probes. A mixture of acetic acid **1a** (0.1 mmol), dodecyl aldehyde **2a** (0.1 mmol) and *p*-methoxybenzyl isocyanide **3a** (0.1 mmol) was stirred at room temperature in corresponding solvent, or in PBS (1 mL) in the presence of corresponding additive. After adding a surfactant (*e.g.,* DODAB) (0.02 mmol) – depending on the reaction mixture – either stable, milky suspensions were obtained (dispersed vesicles), almost transparent solutions (*e.g.,* SDS), or phase separation occurred (*e.g.* PBS). In all cases where significant yields were obtained, product precipitation occurred (see Supporting Information). After 24 h acetonitrile was added to the volume 10 mL. The resulting mixture was analyzed by HPLC (acetonitrile/water 70:30, v/v; flow rate 1 mL/min).

Characterization of compounds 4a-p.

1-(4-Methoxybenzylamino)-1-oxotridecan-2-yl acetate **4a** White powder; mp 77-78 °C; elemental analysis found: C, 70.48; H, 9.34; N, 3.38. Calc. for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.52; N, 3.58;^{1}H NMR (400 MHz; $CDCl_3$) δ_H0.88(3H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$), 1.21-1.35 (18H, br m, 9×C*H*$_2$), 1.80-1.91 (2H, m, C*H*$_2$CH), 2.11 (3H, s, C*H*$_3$CO), 3.90 (3H, s, C*H*$_3$O), 4.34-4.45 (2H, m, C*H*$_2$N), 5.16-5.20 (1H, m, C*H*), 6.23 (1H, t, *J* 5.2 Hz, N*H*), 6.21-6.24 (2H, m, Ph), 7.18-7.20 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.07, 20.96, 22.66, 24.77, 29.23, 29.31, 29.40, 29.49, 29.59, 31.89, 31.93, 42.67, 55.28, 74.22, 114.15, 129.04, 129.96, 159.14, 169.63, 169.69; HRMS calcd. for $C_{23}H_{37}NO_4Na$ $[M+Na]^+$: 414.2620, found: 414.2614.

1-(Benzylamino)-1-oxotridecan-2-yl acetate **4b** White powder; mp 72-73 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.88 (3H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$), 1.19-1.35 (18H, br m, 9×C*H*$_2$), 1.79-1.95 (2H, m, C*H*$_2$CH), 2.12 (3H, s, C*H*$_3$CO), 4.41-4.53 (2H, m, C*H*$_2$N), 5.19-5.22 (1H, m, C*H*), 6.30 (1H, br s, N*H*), 7.25-7.30 (5H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.08, 20.96, 22.66, 24.77, 29.23, 29.31, 29.40, 29.49, 29.59, 31.89, 31.94, 43.18, 74.23, 127.61, 127.66, 128.76, 137.89, 169.65, 169.82; HRMS calcd. for $C_{22}H_{35}NO_3Na$ $[M+Na]^+$: 384.2515, found: 384.2513.

1-(4-Methoxybenzylamino)-1-oxodecan-2-yl acetate **4c** White powder; mp 76-77 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.88 (3H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$), 1.21-1.40 (12H, br m, 6×C*H*$_2$), 1.81-1.92 (2H, m, C*H*$_2$CH), 2.11 (3H, s, C*H*$_3$CO), 3.78 (3H, s, C*H*$_3$O), 4.34-4.46 (2H, m, C*H*$_2$N), 5.17-5.20 (1H, m, C*H*), 6.22 (1H, br s, N*H*), 6.85-6.88 (2H, m, Ph), 7.17-7.20 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.05, 20.97, 22.61, 24.75, 29.14, 29.22, 29.34, 31.80, 31.92, 42.67, 55.28, 74.22, 114.15, 129.04, 129.95, 159.14, 169.71; HRMS calcd. for $C_{20}H_{31}NO_4Na$ $[M+Na]^+$: 372.2151, found: 372.2145.

1-(Benzylamino)-1-oxodecan-2-yl acetate **4d** White powder; mp 62-63 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.88 (3H, t, *J* 6.8 Hz, C*H*$_3$CH$_2$), 1.21-1.39 (12H, br m, 6×C*H*$_2$), 1.80-1.93 (2H, m, C*H*$_2$CH), 2.17 (3H, s, C*H*$_3$CO), 4.43-4.50 (2H, m, C*H*$_2$N), 5.19-5.30 (1H, m, C*H*), 6.28 (1H, br s, N*H*), 7.26-7.31 (5H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.05, 20.95, 22.61, 24.75, 29.13, 29.22, 29.33, 31.79, 33.92, 43.17, 74.21, 127.61, 127.65, 128.75, 137.88, 169.66, 169.82; HRMS calcd. for $C_{19}H_{29}NO_3Na$ $[M+Na]^+$: 342.2045, found: 342.2044.

2-(4-Methoxybenzylamino)-2-oxo-1-phenylethyl acetate **4e** White powder; mp 100-101 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.15 (3H, s, C*H*$_3$CO), 3.79 (3H, s, C*H*$_3$O), 4.34-4.53 (2H, m, C*H*$_2$N), 6.01 (1H, s, C*H*), 6.34 (1H, br s, N*H*), 6.83-6.87 (2H, m, Ph), 7.13-7.16 (2H, m, Ph), 7.35-7.40 (2H, m, Ph), 7.40-7.46 (3H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C20.97, 42.88, 55.28, 75.56, 114.15, 127.38, 128.75, 128.98, 129.05, 135.57, 159.15, 168.11; HRMS calcd. for $C_{18}H_{19}NO_4Na$ $[M+Na]^+$: 336.1212, found: 336.1208.

2-(4-Methoxybenzylamino)-1-(4-nitrophenyl)-2-oxoethyl acetate **4f** White powder; mp 111-111.5 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H2.20 (3H, s, C*H*$_3$CO), 3.80 (3H, s, C*H*$_3$O), 4.35-4.45 (2H, m, C*H*$_2$N), 6.16 (1H, s, C*H*), 6.53 (1H, br s, N*H*), 6.85-6.88 (2H, m, Ph), 7.15-7.17 (2H, m, Ph), 7.61-7.63 (2H, m, Ph), 8.20-8.22 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 20.87, 43.05, 55.30, 74.43, 114.26, 123.82, 128.02, 129.14, 129.34,

142.50, 159.33, 166.83; HRMS calcd. for $C_{18}H_{18}N_2O_6Na$ $[M+Na]^+$: 381.1063, found: 381.1057.

2-(Benzylamino)-1-(4-nitrophenyl)-2-oxoethyl acetate **4g** White powder; mp 123-124 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.20 (3H, s, C*H*$_3$CO), 4.46-4.49 (2H, m, C*H*$_2$N), 6.19 (1H, s, C*H*), 6.58 (1H, br s, N*H*), 7.22-7.25 (2H, m, Ph), 7.30-7.33 (3H, m, Ph), 7.61-7.65 (2H, m, Ph), 8.18-8.23 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 20.88, 43.55, 74.45, 123.85, 127.74, 127.92, 128.03, 128.90, 137.30, 142.45, 166.95; HRMS calcd. for $C_{17}H_{16}N_2O_5Na$ $[M+Na]^+$: 351.0957, found: 351.0952.

1-(4-Methoxybenzylamino)-1-oxotridecan-2-yl benzoate **4h** White powder; mp 90-91 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.87 (3H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$), 1.19-1.36 (16H, br m, 8×C*H*$_2$), 1.36-1.48 (2H, m, C*H*$_2$CH$_2$), 1.97-2.03 (2H, m, C*H*$_2$CH), 3.78 (3H, s, C*H*$_3$O), 4.35-4.48 (2H, m, C*H*$_2$N), 5.44-5.47 (1H, m, C*H*), 6.30 (1H, br s, N*H*), 6.83-6.86 (2H, m, Ph), 7.16-7.18 (2H, m, Ph),7.44-7.48 (2H, m, Ph),7.74-7.61 (1H, m, Ph), 8.03-8.05 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.07, 22.65, 24.95, 29.24, 29.30, 29.38, 29.49, 29.58, 31.88, 32.01, 42.67, 55.26, 74.68, 114.12, 128.60, 128.91, 129.73, 129.99, 133.54, 159.08, 165.41, 169.80; HRMS calcd. for $C_{28}H_{39}NO_4Na$ $[M+Na]^+$: 476.2777, found: 476.2781.

1-(Benzylamino)-1-oxotridecan-2-yl benzoate **4i** White powder; mp 69-70 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.86 (3H, t, *J* 5.6 Hz, C*H*$_3$CH$_2$), 1.21-1.35 (16H, br m, 8×C*H*$_2$), 1.38-1.49 (2H, m, C*H*$_2$CH$_2$), 2.00-2.04 (2H, m, C*H*$_2$CH), 4.46-4.62 (2H, m, C*H*$_2$N), 5.46-5.49 (1H, m, C*H*), 6.37 (1H, br s, N*H*), 7.23-7.33 (5H, m, Ph),7.44-7.48 (2H, m, Ph),7.57-7.62 (1H, m, Ph), 8.03-8.06 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.08, 22.65, 24.95, 29.25, 29.31, 29.39, 29.49, 29.58, 31.89, 32.01, 43.17, 74.69, 127.53, 127.54, 128.62, 128.73, 129.34, 129.74, 133.57, 137.90, 165.43, 169.93; HRMS calcd. for $C_{27}H_{37}NO_3Na$ $[M+Na]^+$: 446.2671, found: 446.2672.

1-(4-Methoxybenzylamino)-1-oxodecan-2-yl benzoate **4j** White powder; mp 80.5-81 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.86 (3H, t, *J* 6.0 Hz, C*H*$_3$CH$_2$), 1.18-1.38 (10H, br m, 5×C*H*$_2$), 1.38-1.49 (2H, m, C*H*$_2$CH$_2$), 1.97-2.03 (2H, m, C*H*$_2$CH), 3.78 (3H, s, CH_3O), 4.35-4.50 (2H, m, C*H*$_2$N), 5.44-5.47 (1H, m, C*H*), 6.31 (1H, br s, N*H*), 6.83-6.85 (2H, m, Ph),7.16-7.19 (2H, m, Ph), 7.44-7.48 (2H, m, Ph), 7.57-7.61 (1H, m, Ph), 8.03-8.05 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.05, 22.60, 24.94, 29.13, 29.23, 29.33, 31.78, 32.00, 42.67, 55.26, 74.67, 114.12, 128.60, 128.91, 129.36, 129.72, 129.99, 133.54, 159.07, 165.41, 169.80; HRMS calcd. for $C_{25}H_{33}NO_4Na$ $[M+Na]^+$: 434.2307, found: 434.2302.

1-(Benzylamino)-1-oxodecan-2-yl benzoate **4k** White powder; mp 69-70 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.86 (3H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$), 1.20-1.42 (10H, br m, 5×C*H*$_2$), 1.42-1.46 (2H, m, C*H*$_2$CH$_2$), 2.00-2.04 (2H, m, C*H*$_2$CH), 4.46-4.52 (2H, m, C*H*$_2$N), 5.46-5.49 (1H, m, C*H*), 6.34-6.44 (1H, m, N*H*), 7.24-7.31 (5H, m, Ph),7.44-7.48 (2H, m, Ph), 7.57-7.61 (1H, m, Ph), 8.03-8.06 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.04, 22.60, 24.95, 29.13, 29.24, 29.32, 31.77, 32.01, 43.15, 74.68, 127.52, 127.53, 128.61, 128.71, 129.34, 129.73, 133.56, 137.90, 165.42, 169.90; HRMS calcd. for $C_{24}H_{31}NO_3Na$ $[M+Na]^+$: 404.2202, found: 404.2201.

2-(4-Methoxybenzylamino)-2-oxo-1-phenylethyl benzoate **4l** White powder; mp 141-142 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H3.77 (3H, s, C*H*$_3$O), 4.04-4.45 (2H, m, C*H*$_2$N), 6.36 (1H, s, C*H*), 6.42 (1H, br s, N*H*), 6.81-6.84 (2H, m, Ph), 7.13-7.15 (2H, m, Ph), 7.36-7.46 (5H, m, Ph), 7.53-7.60 (3H, m, Ph), 8.05-8.08 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 42.91, 55.28, 76.01, 114.15, 127.38, 128.60, 128.82, 128.95, 129.03, 129.23, 129.84, 130.13, 133.62, 135.55, 159.11, 165.02, 168.28; HRMS calcd. for $C_{23}H_{21}NO_4Na$ $[M+Na]^+$: 398.1368, found: 398.1366.

2-(Benzylamino)-2-oxo-1-phenylethyl benzoate **4m** White powder; mp 86-87 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.48-4.52 (2H, m, C*H*$_2$N), 6.38 (1H, s, C*H*), 6.51 (1H, br s, N*H*), 7.20-7.31 (5H, m, Ph),7.31-7.52 (5H, m, Ph), 7.53-7.64 (3H, m, Ph), 8.06-8.09 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 43.37, 76.00, 127.53, 127.58, 128.41, 128.72, 128.82, 129.03, 129.19, 129.83, 130.12, 133.51, 133.62, 135.50, 137.72, 165.01, 168.38; HRMS calcd. for $C_{22}H_{19}NO_3Na$ $[M+Na]^+$: 368.1263, found: 368.1254.

2-(4-Methoxybenzylamino)-1-(4-nitrophenyl)-2-oxoethyl benzoate **4n** White powder; mp 127-128 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.78 (3H, s, CH_3O) 4.42-4.45 (2H, m, C*H*$_2$N), 6.44 (1H, s, C*H*), 6.61 (1H, br s, N*H*), 6.82-6.86 (2H, m, Ph),7.13-7.16 (2H, m, Ph), 7.46-7.50 (2H, m, Ph), 7.61-7.65 (1H, m, Ph), 7.72- 7.75 (2H, m, Ph), 8.05-8.10 (2H, m, Ph), 8.21-8.25 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 43.10, 55.29, 74.79, 114.25, 123.89, 128.05, 128.45, 128.52, 128.83, 129.00, 129.36, 129.83, 134.13, 148.19, 159.27, 164.61, 167.05; HRMS calcd. for $C_{23}H_{20}N_2O_6Na$ $[M+Na]^+$: 443.1219, found: 443.1218.

2-(Benzylamino)-1-(4-nitrophenyl)-2-oxoethyl benzoate **4o** White powder; mp 137-138 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.50-4.52 (2H, m, C*H*$_2$N), 6.46 (1H, s, C*H*), 6.65 (1H, br s, N*H*), 7.22-7.34 (5H, m, Ph), 7.47-7.51 (2H, m, Ph), 7.61-7.66 (1H, m, Ph), 7.72-7.76 (2H, m, Ph), 8.06-8.09 (2H, m, Ph), 8.22-8,26 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 43.56, 74.80, 123.90, 127.57, 127.84, 128.04, 128.44, 128.84, 128.87, 129.83, 134.14, 137.32, 142.38, 148.20, 167.14; HRMS calcd. for $C_{22}H_{18}N_2O_5Na$ $[M+Na]^+$: 413.1113, found: 413.1115.

1-(4-Methoxybenzylamino)-1-oxotridecan-2-yl 2-methylbutanoate **4p** – mixture of diasteromers; White powder; mp 63-64 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.88-0.91 (6H, m, 2×C*H*$_3$CH$_2$), 1.09-1.15 (3H, dd, *J* 7.7 Hz *J* 7.1 Hz, C*H*$_3$CH), 1.18-1.38 (18H, m, 9×CH$_2$), 1.42-1.52 (1H, m, CH3C*H*HCH), 1.60-1.69 (1H, m, CH3CH*H*CH), 1.79-1.92 (2H, m, CH$_3$C*H*$_2$CH$_2$), 2.33-2.48 (1H, m, C*H*CH$_3$), 3.80 (3H, s, C*H*$_3$O), 4.37-4.40 (2H, m, C*H*$_2$N), 5.20-5.29(1H, m, C*H*CH2), 6.18(1H, br s, N*H*), 6.85-6.87 (2H, m, Ph),7.17-7.19 (2H, m, Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 11.46, 11.53, 14.07, 16.44, 16.67, 22.65, 24.77, 26.62, 26.71, 29.18, 29.31, 29.38, 29.47, 29.59, 31.89, 31.90, 41.02, 41.10, 42.70, 42.72, 55.28, 73.72, 114.14, 129.00, 129.01, 129.90, 129.93, 159.14, 169.85, 175.30, 175.32; HRMS calcd. for $C_{26}H_{43}NO_4Na$ $[M+Na]^+$: 456.3090, found: 456.3088.

Notes and references

1 D. Dallinger, C.O. Kappe, *Chem. Rev.*, 2007, **107**, 2563; Y. Jung, R.A. Marcus, *J. Am. Chem. Soc.*, 2007, **129**, 5492; C.J. Li, *Chem. Rev.*, 2005, **105**, 3095; A. Chanda, V.V. Fokin, *Chem. Rev.*, 2009, **109**, 725.

2 D.C. Rideout, R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816; R. Breslow, U. Maitra, D. Rideout, *Tetrahedron Lett.*, 1983, **24**, 1901; R. Breslow, U. Maitra, *Tetrahedron Lett.*, 1984, **25**, 1239; C.J. Li, *Chem. Rev.*, 2005, **105**, 3095; C.J. Li, L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68; S. Minakata, M. Komatsu, *Chem. Rev.*, 2009, **109**, 711; A. Chanda, V.V. Fokin, *Chem. Rev.*, 2009, **109**, 725; R.N. Butler, A.G. Coyne, *Chem. Rev.*, 2010, **110**, 6302; S. Otto, J.B.F.N. Engberts, *Org. Biomol. Chem.*, 2003, **1**, 2809; U.M. Lindstrom, F. Andersson, *Angew. Chem. Int. Ed.*, 2006, **45**, 548; J. Chandrasekhar, S. Shariffskul, W.L. Jorgensen, *J. Phys. Chem. B*, 2002, **106**, 8078; M.R. Dack, *Chem. Soc. Rev.*, 1975, **4**, 211; A. Lubineau, *J. Org. Chem.*, 1986, **51**, 2142; A. Lubineau, J. Auge, Y. Queneau, *Synthesis*, 1994, 741; R. A. Sheldon, *J. Mol. Catal. A-Chem*, 1996, **107**, 75; Y.S. Jung, R.A. Marcus, *J. Am. Chem. Soc.,* 2007, **129**, 5492; M. Singh, S. Fatma, P. Ankit, S.B. Singh, J. Singh, *Tetrahedron Lett.*, 2014, **55**, 525; M. Shiri, M.A. Zolfigol, *Tetrahedron*, 2009, **65**, 587; P.H. Von Hippel, T. Schleich, *Acc. Chem. Res.*, 1969, **2**, 257.

3 T. Dwars, E. Paetzold, G. Oehme, *Angew. Chem. Int. Ed.*, 2005, **44**, 7174.

4 P. Walde, H. Umakoshi, P. Stano, F. Mavelli, *Chem. Commun.*, 2014, **50**, 10177.

5 F.M. Menger, J.U. Rhee, H.K. Rhee, *J. Org. Chem.*, 1975, **40**, 3803; M.S. Goedheijt, B.E. Hanson, J.N.H. Reek, P.C.J. Kamer, P.W.N.M. van Leeuwen, *J. Am. Chem. Soc.*, 2000, **122**, 1650; J.B.F.N. Engberts, M.J. Blandamer, *Chem. Commun.*, 2001, **18**, 1701; S. Balakumar, P. Thanasekaran, E. Rajkumar, K.J. Adikalasamy, S. Rajagopal, R. Ramaraj, T. Rajendran, B. Manimaran, K.L. Lu, *Org. Biomol. Chem.*, 2006, **4**, 352.

6 J. W. Szostak, D. P. Bartel and P. L. Luisi, *Nature*, 2001, **409**, 387; V. Noireaux, A. Libchaber, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 17669; P. Walde, *Bioessays*, 2010, **32**, 296; P. Stano, P. Carrara, Y. Kuruma, T. P. de Souza and P. L. Luisi, *J. Mater. Chem.*, 2011, **21**, 18887; S. Matosevic, *Bioessays*, 2012, **34**, 992.

7 C. Herzog, K. Hartmann, V. Kunzi, O. Kursteiner, R. Mischler, H. Lazar, R. Gluck, *Vaccine*, 2009, **27**, 4381; A. Huckriede, L. Bungener, T. Stegmann, T. Daemen, J. Medema, A. M. Palache, J. Wilschut, *Vaccine*, 2005, **23**, S1/26.

8 T. M. Allen, *Trends Pharmacol. Sci.*, 1994, **15**, 215; G. Gregoriadis, *Trends Biotechnol.*, 1995, **13**, 527; Y. Barenholz, *Curr. Opin. Colloid Interface Sci.*, 2001, **6**, 66; V. P. Torchilin, *Nat. Rev. Drug Discovery*, 2005, **4**, 145.

9 T. Kunitake, Y. Okabata, R. Ando, S. Shinkai, S. Hirakawa, *J. Am. Chem. Soc.*, 1980, **102**, 7877; M.V. Scarpa, P.S. Araujo, S. Schreier, A. Sesso, A.G. Oliveira, H. Chaimovich, I.M. Cuccovia *Langmuir*, 2000, **16**, 993; J. Perez-Juste, F. Hollfelder, A.J. Kirby, J.B.F.N. Engberts, *Org. Lett.*, 2000, **2**, 127.

10 T. Rispens, J.B.F.N. Engberts, *Org. Lett.*, 2001, **3**, 941.

11 Y. Murakami, J. Kikuchi, Y. Hisaeda, K. Nakamura, T. Kitazaki, H Kaya, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2339.

12 R. Ueoka, Y. Matsumoto, R.A. Moss, A. Sugii, K. Harada, J. Kikuchi, Y. Murakami, *J. Am. Chem. Soc.*, 1988, **110**, 1588; K. Ohkubo, *Macromol. Rapid Commun.*, 1996, **17**, 109.

13 G. Lu, C. Cai, *Catal. Commun.*, 2010, **11**, 745; A. Kumar, M.K. Gupta, M. Kumar, D. Saxena, *RSC Adv.*, 2013, **3**, 1673.

14 C.S. McKay, D.C. Kennedy, J.P. Pezacki, *Tetrahedron Lett.*, 2009, **50**, 1893.

15 A. Kumar, M.K. Gupta, M. Kumar, *Tetrahedron Lett.*, 2010, **51**, 1582.

16 J. Ghosh, P. Biswas, T. Sarkar, M.G.B. Drew, C. Bandyopadhyay, *Tetrahedron Lett.*, 2014, **55**, 2924.

17 P.K. Sahu, P.K. Sahu, D.D. Agrwal, *RSC Adv.*, 2014, **4**, 40414.

18 A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.*, 2000, **39**, 3168.

19 W. Qu, Z. Zha, K. Ploessl, B.P. Lieberman, L. Zhu, D.R. Wise, C.B. Thompson, H.F. Kung, *J. Am. Chem. Soc.*, 2011, **133**, 1122; A. Zajdlik, Z. Wang, J.L. Hickey, A. Aman, A.D. Schimmer, A.K. Yudin, *Angew. Chem. Int. Ed.*, 2013, **52**, 8411; D. Koszelewski, A. Redzej, R. Ostaszewski, *J. Mol. Catal. B-Enzym.*, 2007, **47**, 51; S. Wang, M. Wang, D. Wang, J. Zhu, *Angew. Chem. Int. Ed.*, 2007, **47**, 388.

20 M.C. Pirrung, K. Das Sarma, *J. Am. Chem. Soc.*, 2003, **126**, 444; E. Vessally, A. Ramazani, E. Yaaghubi, *Monatsh. Chem.*, 2011, **142**, 1143; J. Taran, A. Ramazani, S.W. Joo, K. Slepokura, T. Lis, *Helv. Chim. Acta*, 2014, **97**, 1088.

21 E. Tasca, G. La Sorella, L. Sperni, G. Strukul, A. Scarso, *Green Chem.*, 2015, **17**, 1414; G. La Sorella, G. Strukul, A. Scarso, *Green Chem.*, 2015, **17**, 644; I.T. Horvath, P.T. Anastas, *Chem. Rev.*, 2007, **107**, 2167.

22 M. Passerini, *Gazz. Chim. Ital.*, 1923, **53**, 331; M. Bos, E. Riguet, *J. Org. Chem.*, 2014, **79**, 10881.

23 R. Bossio, *Synthesis*, 1993, **783**, 1.

24 W. Szymański, R. Ostaszewski, *Tetrahedron*, 2008, **64**, 3197.

25 W. Szymański, M. Zwolińska, R. Ostaszewski, *Tetrahedron*, 2007, **63**, 7647.

26 W. Szymański, R. Ostaszewski, *Tetrahedron: Asymmetry.*, 2006, **17**, 2667.

27 A. Brodzka, D. Koszelewski, R. Ostaszewski J. Mol. Catal. B-Enzym., 2012, 82, 96; A. Żądło, D. Koszelewski, F. Borys, R. Ostaszewski, *ChemBioChem*, 2015, **16**, 677.

28 S. Kłossowski, A. Brodzka, M. Zysk, R. Ostaszewski, *Tetrahedron: Asymmetry.*, 2014, **25**, 435; W. Szymański, M. Zwolińska, S. Kłossowski, I. Młynarczuk-Biały, Ł. Biały, T. Issat, J. Malejczyk, R. Ostaszewski, *Bioorgan. Med. Chem.*, 2014, **22**, 1773.

29 S. Kłossowski , B. Wiraszka , S. Berłożecki, R. Ostaszewski, *Org. Lett.*, 2013, **15**, 566.

30 P. Walde, Curr. *Opin. Colloid. Interface Sci.*, 1996, **1**, 638; P. Walde, S. Ichikawa, *Biomol. Eng.*, 2001, **18**, 143; P. Walde, K. Cosentino, H. Engel, P. Stano, *ChemBioChem*, 2010, **11**, 848.

31 T. Kunitake, Y. Okahata, K. Tamaki, F. Kumamaru, M. Takayanagi, *Chem. Lett.*, 1977, **6**, 387; E. Feitosa, P. C. A. Barreleiro, G. Olofsson, *Chem. Phys. Lipids*, 2000, **105**, 201; R. O. Brito, E. F. Marques, *Chem. Phys. Lipids*, 2005, **137**, 18.

32 S. F. Clancy, P. H. Steiger, D. A. Tanner, M. Thies, H. H. Paradies, *J. Phys. Chem.*, 1994, **98**, 11143; M. Thies, S. F. Clancy, H. H. Paradies, *J. Phys. Chem.*, 1996, **100**, 9881.

33 L. Banfi, R. Riva, *Organic Reactions*, ed. L. E. Overman et al., John Wiley & Sons, Inc., Weinheim, 2005, vol. 65, ch. 1, pp 4-5.

34 R. Ramozzi, K. Morokuma, *J. Org. Chem.*, 2015, **80**, 5652.

35 R.V. Ulijn, A.E.M. Jannsen, B.D. Moore, P.J. Halling, *Chem-Eur. J.*, 2001, **7**, 2089; W. Zhang, J.S. Moore, *J. Am. Chem. Soc.*, 2004, **126**, 12796.