(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 January 2018 (18.01.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/011696 A1

(51) International Patent Classification:
B01J 31/02 (2006.01) *B01J 31/24* (2006.01)
B01J 31/18 (2006.01) *C07C 231/02* (2006.01)
B01J 31/22 (2006.01)

(21) International Application Number:
PCT/IB2017/054139

(22) International Filing Date:
10 July 2017 (10.07.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/CN2016/089854
13 July 2016 (13.07.2016) CN

(71) Applicant: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, 4056 Basel (CH).

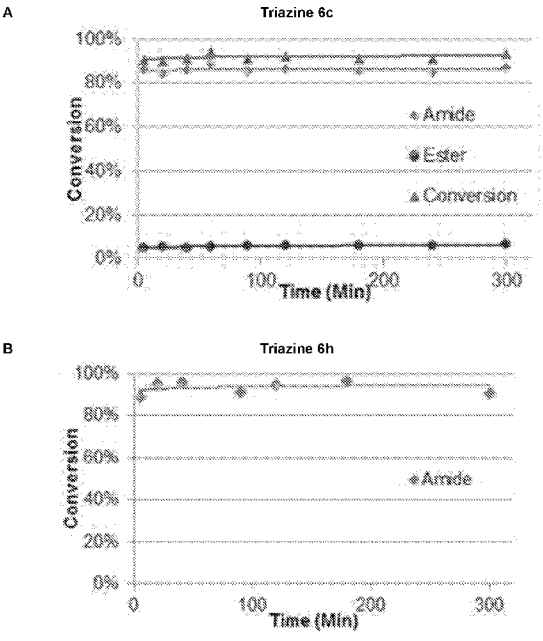
(72) Inventors: **GALLOU, Fabrice**; c/o Novartis Pharma AG, Postfach, 4002 Basel (CH). **GUO, Pengfei**; c/o Suzhou Novartis Pharma Technology Co., Ltd., #18 Tonglian Road Riverside Industrial Park, Changshu Economic Development Zone, Changshu, Jiangsu 215537 (CN). **ZHOU, Jianguang**; c/o SUZHOU NOVARTIS PHARMA TECHNOLOGY CO., LTD., No. 18 Tonglian Road, Yanjiang Industrial Park, Economic Development Zone, Changshu City, Jiangsu 215537 (CN). **PARMENTIER, Michael**; c/o Novartis Pharma AG, Postfach, 4002 Basel (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

(54) Title: CATALYSTS FOR CHEMICAL REACTIONS IN A WATER-SURFACTANT MIXTURE

Figure 1



(57) Abstract: The present invention is directed to reaction mixtures comprising a water-surfactant mixture, wherein the catalyst comprises a compound with solubilizing groups. This technology improves the solubility of the reaction components in the water-surfactant mixture and thereby, greatly increases the productivity and selectivity of the chemical reaction.

WO 2018/011696 A1

[Continued on next page]

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

"Catalysts for chemical reactions in a water-surfactant mixture"

FIELD OF THE INVENTION

The present invention is directed to improvements of chemical reactions using surfactant-water reaction media. Solubility of the reaction components is increased by catalyst compounds modified with solubilizing groups. Thereby, yield and selectivity of the chemical reaction is greatly enhanced. Hence, the present invention pertains to chemical reaction mixtures comprising respectively modified catalyst compounds and a surfactant-water mixture.

BACKGROUND OF THE INVENTION

The identification of sustainable harmless solvent to be used for general purposes has been an area of focus by many chemistry groups globally in the last few decades. It became all the more important as not only the well-known ozone-depleting chlorinated solvents were flagged many years ago, but also when the reprotoxicity of such frequently used polar aprotic solvents as DMF, DMAC or NMP was made visible. To tackle this particular topic, a variety of more or less general strategies were followed by multiple groups around the world, developing neoteric solvents for example, which will have given rise to such solvents as the bio-based cyrene, or such ethers as CPME or the more powerful MeTHF, other harmless derivatives of problematic solvents developed directly by chemical producers, ionic liquids, or more sophisticated systems utilizing compressed gases or phase-transfer catalysis, switchable solvents, and fluorous systems. While punctual success stories can be found and have proven tremendous benefits at times, the generality is however lagging behind. This unfortunately did not yet lead to the required dramatic change in mindset. For example, time-critical experimentations continue relying on the most established undesirable DMF or NMP for example. This is all the more critical and relevant in the pharmaceutical industry where the physical properties of the target compounds routinely display limited solubility.

One approach towards the replacement of undesirable polar aprotic solvents was developed by Professor Lipshutz, disclosing his latest application on the benign-by-design surfactant chemistry.

However, there is a need in the art to improve the chemical reactions in the surfactant solvent systems to increase productivity and reduce unwanted side products.

SUMMARY OF THE INVENTION

The present invention is based on the findings that in reaction mixtures using a surfactant-water mixture as reaction medium, solubilizing groups attached to the catalyst compounds greatly enhance solubilization of the reaction partners. This has a huge impact on the productivity as well as the selectivity of the reaction. Especially alkyl groups and poly(ethylene glycol) groups of medium length show highly promising results when attached to coupling reagents or complexing ligands of metal catalysts.

In a first aspect, the present invention provides a reaction mixture comprising one or more reactants, a catalyst and a surfactant-water mixture, wherein the catalyst is (a) a coupling reagent comprising one or more solubilizing groups; or (b) a metal ion in complex with a ligand comprising one or more solubilizing groups; wherein the solubilizing group comprises a C5-50 alkyl group or a poly(alkylene glycol) group with 2 to 20 repeating units.

In a second aspect, the present invention provides a method of performing a chemical reaction, comprising the steps of

(a) providing a reaction mixture according to the first aspect of the invention, and

(b) allowing the chemical reaction to proceed.

In a third aspect, the present invention provides a method of increasing the yield of a chemical reaction, and/or decreasing the amount of side products produced in a chemical reaction, wherein the chemical reaction is performed in a surfactant-water mixture, comprising the steps of

(a) providing a reaction mixture comprising one or more reactants, a catalyst, and a surfactant-water mixture, wherein the catalyst is a coupling reagent comprising one or more solubilizing groups, or a metal ion in complex with a ligand comprising one or more solubilizing groups; wherein the solubilizing group comprises a C_{5-50} alkyl group or a poly(alkylene glycol) group with 2 to 20 repeating units; and

(b) allowing the chemical reaction to proceed.

The above aspects can be combined. Other objects, features, advantages and aspects of the present invention will become apparent to those skilled in the art from the

following description and appended claims. It should be understood, however, that the following description, appended claims, and specific examples, which indicate preferred embodiments of the application, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides, in a first aspect, a reaction mixture comprising one or more reactants, a catalyst and a surfactant-water mixture, wherein the catalyst is (a) a coupling reagent comprising one or more solubilizing groups; or (b) a metal ion in complex with a ligand comprising one or more solubilizing groups; wherein the solubilizing group comprises a C5-50 alkyl group or a poly(alkylene glycol) group with 2 to 20 repeating units.

The inventive technology is suitable for all chemical reactions which can be performed in a medium comprising a surfactant-water mixture. It can in particular be used in organic chemistry, for example with at least partly hydrophobic compounds. Exemplary suitable chemical reactions include chemical reactions selected from the group consisting of cross-coupling reactions such as Suzuki cross-coupling, Suzuki-Miyaura cross-coupling, Sonogashira cross-coupling, Heck cross-coupling, Buchwald-Hartwig cross-coupling, Negishi cross-coupling, Stille cross-coupling, Miyaura borylation, Hiyama cross-couplings, Chan-Ma cross-coupling, and olefin metathesis; copper-mediated cross-couplings, nickel-mediated cross-couplings, nucleophilic substitutions such as nucleophilic aromatic substitution (S_NAr); electrophilic halogenation, aromatic and heteroaromatic halogenation; biocatalytic transformations; amidation; oxidation; reduction such as reduction of nitro groups, oxime groups, azide groups, nitrile groups and amide groups; nitrile and imine hydrolysis; hydrogenation and debenzylation. In certain embodiments, the chemical reaction is an amidation. In these embodiments, the catalyst preferably is a coupling reagent. The reactants and the catalyst present in the reaction mixture are suitable for the specific chemical reaction. In particular, the reactants and the catalyst are specifically chosen so that the chemical reaction can be performed.

The surfactant in the surfactant-water mixture can be any surfactant. In particular, the surfactant should not interfere with the chemical reaction. In certain embodiments, the surfactant is a non-ionic surfactant. The surfactant generally is amphiphilic and comprises a hydrophilic part and a hydrophobic part. In specific embodiments, the surfactant is able to form micelles in the surfactant-water mixture.

In certain embodiments, the hydrophilic part of the surfactant comprises a polyalkylene glycol moiety, especially a polyethylene glycol moiety or a polypropylene glycol moiety. The polyalkylene moiety, especially the polyethylene glycol moiety, may have an average molecular weight in the range of about 100 to about 10,000 g/mol, especially in the range of about 300 to about 3,000 g/mol, in particular in the range of about 400 to about 2,000 g/mol. Certain examples of surfactants comprising a polyalkylene glycol moiety include tocopherol polyethylene glycol succinates (TPGS), in particular DL-α-tocopherol polyethylene glycol succinates such as TPGS-750-M, TPGS-1000, TPGS-1500, TPGS-400, TPGS-1100-M, TPGS-2000, TPGS-860-oleate, TPGS-PEG-PPG-PEG-1100 and TPGS-PPG-PEG—70-butyl, and DL-α-tocopherol polypropylene glycol succinates such as TPPG-1000 and TPPG-1000-butyl; Triton X-100; polyethylene glycol alkyl ethers such as Brij surfactants, in particular Brij 30, Brij 35, Brij 52, Brij 56, Brij 58, Brij 72, Brij 76, Brij 78, Brij 92, Brij 96, Brij 98, Cremophor A6, Cremophor A25 and Thesit; polyethylene glycol esters such as polyethylene glycol (15)-hydroxystearate (Solutol HS 15); polyethylene glycol sorbitan fatty acid esters, also known as polysorbates or Tween, such as polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85 and polysorbate 120; cholesteryl PEG succinates such as holesteryl PEG1000 succinate; (deoxy) cholic PEG such as colic PEG1000 and deoxy-cholic PEG1000; chromanol polyethylene glycol succinates such as Chrom-400 and Chrom-1000; b-sitosterol methoxyethyleneglycol succinate (Nok); and other derivatives of PEG such as C4-azo-PEG. In specific embodiments, the surfactant is a DL-α-tocopherol polyethylene glycol succinate, in particular TPGS-750-M.

Furthermore, also other surfactants can be used, including, for example, cetyltrimethylammonium bromide (CTAB); phase transfer surfactants (PTS) such as sodium deoxycholate; polyoxyethanyl ubiquinol sebacate (PQS) and functionalized PQS; and octanoic acid and other long alkyl chain acids, in particular C6 – C20 alkyl chain acids.

The concentration of the surfactant in the surfactant-water mixture in particular is in the range of 0.1 to 10% (w/w). In certain embodiments, the concentration of the surfactant in the surfactant-water mixture is in the range of 0.5 to 5% (w/w), especially in the range of 0.8 to 4% (w/w), 1 to 3% (w/w) or 1.5 to 2.5% (w/w), such as about 2% (w/w). In specific embodiments, the concentration of the surfactant in the surfactant-water mixture is above its critical micellar concentration.

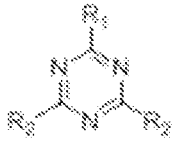
The catalyst in the reaction mixture is a coupling reagent comprising one or more solubilizing groups or a metal ion in complex with a ligand comprising one or more solubilizing groups. Suitable catalysts and ligands are known in the art and can readily be selected by a person skilled in the art. The coupling reagent or metal ion in complex

with a ligand is not restricted to specific compounds as long as it is suitable for catalyzing the chemical reaction of the reactants into the desired product. Hence, the choice of the catalyst depends on the type of chemical reaction to be performed in the reaction mixture.

In embodiments wherein the catalyst is a coupling reagent, it is in particular a coupling reagent for amide formation. Especially, it may be selected from the group consisting of (i) coupling reagents for coupling via activated ester such as carbodiimides, in particular N,N'-dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide and 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide, phosphonium salts, in particular (benzotriazol-1-yloxy)-tris(dimethylamino)-phosphonium hexafluorophosphate and (benzotriazol-1-yloxy)-tris(pyrrolidine)-phosphonium hexafluorophosphate, guanidinium and uronium salts, in particular N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate, N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-yl-methylene]-N-methylmethan-aminium hexafluorophosphate N-oxide, N-[(1H-benzotriazol-1-yl)(dimethylamino)methylene]-N-methylmethanaminium tetrafluoroborate N-oxide, 2-(2-oxo-1(2H)-pyridyl-1,1,3,3-tetramethyluronium tetrafluoroborate and O-[(cyano(ethoxycarbonyl)-methyleneamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate, and triazine compounds, in particular cyanuric chloride, 2-chloro-4,6-dimethoxy-1,3,5-triazine and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride; and (ii) coupling reagents for coupling via boron species such as boric acid and 3-nitrophenylboronic acid.

In certain embodiments, the coupling reagent is a 1,3,5-triazine derivative. The 1,3,5-triazine derivative may comprise a quaternary amine which in particular may be attached to the 2-position of the triazine ring. The quaternary amine may be formed by a trialkylamino group such as a trimethylamino group, or an N-alkyl-N-morpholino group such as an N-methyl-N-morpholino group, attached to the triazine ring. Furthermore, the 1,3,5-triazine derivative may be substituted with methyl, ethyl, propyl, methoxy, ethoxy and/or propoxy, in particular at the 4- and/or the 6-position of the triazine ring. In certain embodiments, the one or more solubilizing groups are attached to the quaternary amine and/or the 4- and/or 6-position of the triazine ring.

In specific embodiments, the coupling reagent has the general formula (I)



(I)

wherein

R_1 is $-N^+(R_3)_3$;

each of R_2 is independently C1-5 alkoxy, C1-5 alkyl, hydroxy, amino optionally substituted with one or two C1-5 alkyl, or $-N^+(R_3)_3$, wherein the C1-5 alkyl or alkoxy group is optionally substituted with one or two groups selected from hydroxy, amino, methoxy and ethoxy, and/or wherein optionally one or two carbon atoms are replaced by oxygen, sulfur or nitrogen;

each of R_3 is independently C1-5 alkyl optionally substituted with one or two groups selected from hydroxy, amino, methoxy and ethoxy, and/or wherein optionally one or two carbon atoms are replaced by oxygen, sulfur or nitrogen, and wherein two R_3 groups may optionally form a C4-7 heterocycle with the nitrogen atom to which they are attached, wherein optionally one or two carbon atoms are replaced by oxygen, sulfur or nitrogen;

and wherein at least one of R_2 and/or R_3 is replaced by a solubilizing group.

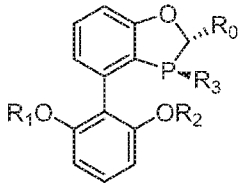
In certain embodiments, R_1 is $-N^+(R_3)_3$, wherein all of R_3 are methyl. In these embodiments, preferably one of the R_3 groups is replaced by a solubilizing group and in particular both of R_2 are methoxy. In other embodiments, R_1 is $-N^+(R_3)_3$, wherein one of R_3 is methyl and the other two of R_3 together with the nitrogen form a morpholine ring. In these embodiments, preferably at least one and in particular both of the R_2 groups are replaced by a solubilizing group. In these embodiments, the R_2 group not replaced by a solubilizing group in particular is methoxy or N-methylmorpholin-4-yl.

In certain embodiments, charged coupling reagents further comprise a counter ion such as chloride, bromide, iodide, hexafluorophosphate or tetrafluoroborate.

In certain embodiments the catalyst is an amide coupling reagent such as a triazine compound. In these embodiments, the reaction mixture is in particular used for an amidation reaction. In these embodiments, the reaction mixture preferably comprises a carboxylic acid and an amine as reactants. In other embodiments, the triazine compound is used as a coupling reagent in a selective reduction or a cross-coupling reaction with an organo-metallic compound.

In embodiments wherein the catalyst is a metal ion in complex with a ligand, the metal ion may be selected from the group consisting of copper ion, ruthenium ion, rhodium ion, palladium ion, nickel ion, zinc ion, gold ion, manganese ion, iron ion and cobalt ion. The ligand may be any ligand suitable for complexing the metal ion. It may be selected from the group consisting of biphenyl compounds; carbene compounds such as N-heterocyclic carbenes, in particular 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; bi-N-heteroaromatic compounds such as bipyridine compounds.

In specific embodiments, the ligand is a biphenyl compound having the general formula (II)



(II)

wherein

R_1, R_2 and R_3 are independently of each other hydrogen or C1-5 alkyl optionally substituted with one or two groups selected from hydroxy, amino, methoxy and ethoxy, and/or wherein optionally one or two carbon atoms are replaced by oxygen, sulfur or nitrogen;

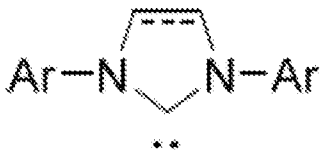
R_0 is H, or C1-5 alkyl, in particular methyl, or CH_2-Ar, wherein Ar is a phenyl or benzyl optionally substituted with 1, 2, 3, 4 or 5 R_4, and wherein the C1-5 alkyl group is optionally substituted with one or two groups selected from hydroxy, amino, methoxy and ethoxy, and/or wherein optionally one or two carbon atoms are replaced by oxygen, sulfur or nitrogen;

each R_4 is independently of each other C1-5 alkoxy, C1-5 alkyl, poly(ethylene glycol) with 2, 3 or 4 repeating units, poly(propylene glycol) with 2, 3 or 4 repeating units, hydroxy or amino optionally substituted with one or two C1-5 alkyl, wherein the C1-5 alkyl or alkoxy group is optionally substituted with one, two or three groups selected from hydroxy, halogen, amino, methoxy and ethoxy, and/or wherein optionally one or two carbon atoms are replaced by oxygen, sulfur or nitrogen, and wherein the poly(ethylene glycol) and poly(propylene glycol) is optionally substituted with methyl, ethyl or propyl at the terminal oxygen;

and wherein at least one of R_0, R_1, R_2 and R_4, preferably at least one of R_1 and R_2, especially both of R_1 and R_2, is replaced by a solubilizing group.

In certain embodiments, Ar is phenyl substituted with electron- or electron-withdrawing groups such as isopropyl or trifluoromethyl groups. For example, Ar may be 2,4,6-tris-isopropyl phenyl or 3,5-bis-trifluoromethyl phenyl. Furthermore, R_3 preferably is tertiary butyl. R_1 and R_2, if not replaced by a solubilizing group, preferably are methyl.

In further embodiments, the ligand is an N-heterocyclic carbene compound having the general formula (III)



(III)

wherein

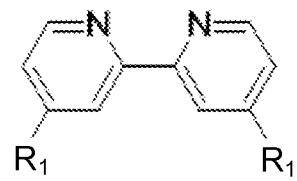
each Ar is independently from each other a phenyl optionally substituted with 1, 2, 3, 4 or 5 R_1;

each R_1 is independently of each other C1-5 alkoxy, C1-5 alkyl, poly(ethylene glycol) with 2, 3 or 4 repeating units, poly(propylene glycol) with 2, 3 or 4 repeating units, hydroxy or amino optionally substituted with one or two C1-5 alkyl, wherein the C1-5 alkyl or alkoxy group is optionally substituted with one or two groups selected from hydroxy, amino, methoxy and ethoxy, and/or wherein optionally one or two carbon atoms are replaced by oxygen, sulfur or nitrogen, and wherein the poly(ethylene glycol) and poly(propylene glycol) is optionally substituted with methyl, ethyl or propyl at the terminal oxygen;

and wherein at least one of the R_1 groups, preferably one R_1 on each Ar group is replaced by a solubilizing group.

In specific embodiments, each Ar is phenyl substituted with three R_1 in 2-, 4- and 6-position, wherein each R_1 is methyl, and wherein at least one R_1, especially one R_1 on each Ar, is replaced by a solubilizing group.

In further embodiments, the ligand is a bipyridine compound having the general formula (IV)



(IV)

wherein

each R_1 is independently of each other C1-5 alkoxy, C1-5 alkyl, poly(ethylene glycol) with 2, 3 or 4 repeating units, poly(propylene glycol) with 2, 3 or 4 repeating units, hydroxy or amino optionally substituted with one or two C1-5 alkyl, wherein the C1-5 alkyl or alkoxy group is optionally substituted with one or two groups selected from hydroxy, amino, methoxy and ethoxy, and/or wherein

optionally one or two carbon atoms are replaced by oxygen, sulfur or nitrogen, and wherein the poly(ethylene glycol) and poly(propylene glycol) is optionally substituted with methyl, ethyl or propyl at the terminal oxygen;

and wherein at least one of the R_1 groups, preferably both R_1 groups are replaced by a solubilizing group.

In specific embodiments, one R_1 is methoxy and the other is replaced by a solubilizing group, or both of R_1 are replaced by a solubilizing group.

The concentration of the catalyst in the reaction mixture is selected so that it is able to catalyze the desired chemical reaction. In embodiments wherein the catalyst is a metal ion in complex with a ligand, suitable catalyst concentrations are for example 0.1 to 25 mol%, especially 1 to 20 mol%, 3 to 15 mol% or 5 to 10 mol%, with respect to the molar amount of one or more of the reactants. In embodiments wherein the catalyst is a coupling reagent, the catalyst is present in stoichiometric amounts. In particular, the concentration of the coupling reagent is 75 to 250 mol%, especially 90 to 200 mol%, 100 to 150 mol% or 110 to 130 mol %, with respect to the molar amount of one or more of the reactants.

The coupling reagent or ligand comprises one or more solubilizing groups. That is, the coupling reagent or ligand comprises one, two, three, four, five or more solubilizing groups. In one embodiment, the coupling reagent or ligand comprises one solubilizing group. In another preferred embodiment, the coupling reagent or ligand comprises two solubilizing groups. In embodiments wherein the coupling reagent or ligand comprises more than one solubilizing group, the solubilizing groups may be different or the same, and in particular are the same. Each of the solubilizing groups comprises a C_{5-50} alkyl group or a poly(alkylene glycol) group with 2 to 20 repeating units. The solubilizing groups are attached to the remaining part of the coupling reagent or ligand via a covalent bond or a functional group such as an ether group, an ester group, an amine group, an amide group, a thioether group, a thioester group, or a thioamide group.

In specific embodiments, the solubilizing group comprises a C_{5-50} alkyl group. The alkyl group may be linear or branched or cyclic and in particular is linear. The alkyl group has 5 to 50 carbon atoms, in particular 5 to 25 carbon atoms, preferably 6 to 20 carbon atoms, 7 to 18 carbon atoms, 8 to 15 carbon atoms or 10 to 14 carbon atoms, especially about 12 carbon atoms. The alkyl group of the solubilizing group may be substituted with one or more groups selected from methoxy, ethoxy, propoxy, hydroxy, and amino optionally substituted with one or two of methyl, ethyl and/or propyl, in particular methoxy, ethoxy or hydroxy, and/or one or more carbon atoms, in particular one, two, three or four carbon atoms, may be replaced by oxygen, sulfur or nitrogen. In certain embodiments, the solubilizing group is a linear C8-40 alkyl attached to the

remaining part of the coupling reagent or ligand via an ether group and optionally substituted with a methoxy group at its terminal end. Suitable examples of the solubilizing group include 12-methoxy-n-dodecyloxy and n-dodecyloxy.

In further embodiments, the solubilizing group comprises a poly(alkylene glycol) group with 2 to 20 repeating units. The poly(alkylene glycol) in particular is a poly(ethylene glycole), poly(propylene glycol) or poly(butylene glycol), preferably a poly(ethylene glycole). The poly(alkylene glycol) group may have 2 to 15 repeating units, in particular 2 to 12 repeating units, 3 to 10 repeating units, 3 to 8 repeating units, or 4 to 6 repeating units, especially about 5 repeating units. The poly(alkylene glycol) group may be substituted with one or more groups selected from methyl, ethyl, propyl, methoxy, ethoxy, propoxy, hydroxy, and amino optionally substituted with one or two of methyl, ethyl and/or propyl, in particular methyl, ethyl or propyl. In certain embodiments, the poly(alkylene glycol) group is substituted at the terminal oxygen, in particular with methyl or ethyl. In further embodiments, the poly(alkylene glycol) group comprises the same substitution at each repeating unit, in particular a methyl or ethyl group. Suitable examples of the solubilizing group include poly(ethylene glycol) with 4 to 6 repeating units and optionally a methyl group at the terminal oxygen.

The one or more reactants in the reaction mixture may be any reactants suitable for performing the chemical reaction. The reactants in particular depend on the type of chemical reaction which is to be performed in the reaction mixture. In certain embodiments, the reaction mixture comprises one reactant, two reactants or three reactants. In specific embodiments, at least one of the reactants is not water-miscible or only partly water-miscible. A reactant which is only partly water-miscible in particular is only miscible with water at a concentration of 20 g/l or less, especially 10 g/l or less or 5 g/l or less, at room temperature. Exemplary reactants include boronic acids, boronate esters, organosilanes, halides, acids and/or corresponding activated esters, amines, alcohols and alkenes. In embodiments wherein the reaction mixture is for performing an amidation reaction, the reaction mixture in particular comprises one reactant being a carboxylic acid and one reactant being an amine, especially a primary amine.

The reactants can be used in any concentration which is feasible for performing the chemical reaction. In particular, the reactants are used at high concentrations. For example, the concentration of at least one of the reactants, especially of all reactants, in the reaction mixture is at least 0.1 M, in particular at least 0.5 M, at least 1.0 M, at least 1.1 M, at least 1.2 M, at least 1.3 M, at least 1.5 M, at least 1.7 M or at least 2.0 M. In certain embodiments wherein the reaction mixture additionally comprises an organic solvent, the concentration of one or more of the reactants in the reaction mixture is above the saturation concentration of its solubility or miscibility in the

surfactant-water mixture. In particular, it is at least about 5%, especially at least about 10%, at least about 20%, at least about 30% or at least about 50% above said saturation concentration. In these embodiments, solubility or miscibility of the reactants is provided by the organic solvent in the reaction mixture. The person skilled in the art is able to select suitable reactants and their concentrations.

In certain embodiments, the reaction mixture may additionally comprise a base. The presence of the additional base in the reaction mixture in particular depends on the type of chemical reaction which is to be performed in the reaction mixture. The base may be an organic base or an inorganic base. In particular, the base is at least partly water-soluble or at least partly water-miscible. Exemplary bases include trialkylamines such as triethylamine (TEA), N-methylmorpholine (NMM), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), K_3PO_4, $NaHCO_3$ and Na_2CO_3. The concentration of the base in the reaction mixture in particular is in the range of 0.5 to 10 molar equivalents of one of the reactants, especially in the range of 0.9 to 6, 1.0 to 5, 1.2 to 4 or 1.5 to 3.5 molar equivalents of one of the reactants. If the reaction mixture is for performing a chemical reaction which does not need a base, the reaction mixture does not have to contain a base.

In specific embodiments, the reaction mixture further comprises an organic solvent. The organic solvent in the reaction mixture may be any organic solvent. Preferably, it shall not disturb or inhibit the chemical reaction and in particular shall increase the homogeneity of the reaction mixture. In certain embodiments, the organic solvent is water-miscible or partly water-miscible. The organic solvent especially is an aprotic organic solvent. Suitable examples of the organic solvent include acetone, tetrahydrofuran (THF) and derivatives thereof such as methyl tetrahydrofuran, pyridine, polyethylene glycol (PEG), polypropylene glycol (PPG), in particular PEG with an average molecular weight of about 100 g/mol to about 2000 g/mol such as PEG200, PEG600, PEG1000 and PEG2000, derivatives thereof such as mono- or dialkyl PEG, in particular mono- or dimethyl PEG, mono- or diethyl PEG and mono- or dipropyl PEG. Further examples include acetonitrile, dimethylformamide (DMF), dichloromethane (DCM), toluene, and alcohols such as a C_{1-10} aliphatic alcohol, in particular 2-butyl alcohol. In certain embodiments, the organic solvent is not a base and/or does not act as base in the chemical reaction.

In specific embodiments, an organic solvent is used which increases the viscosity of the reaction mixture. For example, the viscosity of the reaction mixture containing the organic solvent is at least 1.25 cSt, especially at least 1.5 cSt, at least 1.75 cSt or at least 2.0 cSt. Suitable organic solvents which increase the viscosity of the reaction mixture include PEGs such as PEG200, PEG600 and PEG1000 (PEG with an average molecular weight of 200 g/mol, 600 g/mol and 1000 g/mol, respectively).

In specific embodiments, the reaction mixture comprises 0.1 to 50 volume equivalents of the organic solvent and 1 to 50 volume equivalents of the surfactant-water mixture per mass of the reactants or product, respectively. The amount of the organic solvent and the amount of the surfactant-water mixture are defined in relation to the amount of the theoretical product or alternatively the reactants of the chemical reaction. In case the amount is defined based on the theoretical product, 1 volume equivalent equals the total weight of the theoretical product obtained by 100% conversion in the chemical reaction. The weight of the theoretical product is converted into volume using a theoretical density of 1 g/ml. Hence, if for example 1.5 kg product is calculated based on 100% conversion, 1 volume equals 1.5 l. In case the amount is defined based on the reactants, 1 volume equivalent equals the total weight of the reactants. The weight of the reactants is converted into volume using a theoretical density of 1 g/ml. Hence, if for example 1.5 kg reactants are used in the reaction mixture, 1 volume equals 1.5 l.

In certain embodiments, the amount of the organic solvent in the reaction mixture is at least 0.2 volume equivalents, in particular at least 0.4 volume equivalents, at least 0.6 volume equivalents, at least 0.8 volume equivalents, at least 1.0 volume equivalent, at least 1.5 volume equivalents, or at least 2.0 volume equivalents. In further embodiments, the amount of the organic solvent in the reaction mixture is at most 40 volume equivalents, in particular at most 30 volume equivalents, at most 25 volume equivalents, at most 20 volume equivalents, at most 15 volume equivalents, at most 12 volume equivalents, or at most 10 volume equivalents. In specific embodiments, the amount of the organic solvent in the reaction mixture is in the range of 0.4 to 25 volume equivalents, in particular 0.8 to 15 volume equivalents. In certain embodiments, the amount of the organic solvent in the reaction mixture is in the range of from 1% to 70%, in particular from 2% to 65%, from 3% to 60%, from 4% to 55% or from 5% to 50%.

In certain embodiments, the amount of the surfactant-water mixture in the reaction mixture is at least 1.5 volume equivalents, in particular at least 2.0 volume equivalents, at least 2.5 volume equivalents, at least 3.0 volume equivalents, at least 3.5 volume equivalents, at least 4.0 volume equivalents, or at least 5.0 volume equivalents. In further embodiments, the amount of the surfactant-water mixture in the reaction mixture is at most 45 volume equivalents, in particular at most 40 volume equivalents, at most 35 volume equivalents, at most 30 volume equivalents, at most 25 volume equivalents, at most 22 volume equivalents, or at most 20 volume equivalents. In specific embodiments, the amount of the surfactant-water mixture in the reaction mixture is in the range of 1.5 to 25 volume equivalents, in particular 2.0 to 20 volume equivalents. In certain embodiments, the amount of the surfactant-water mixture in the reaction mixture is in the range of from 30% to 98%, in particular from 35% to 95%, from 40% to 92%, from 45% to 90% or from 50% to 85%.

The amount of organic solvent and surfactant-water mixture together in particular may in certain embodiments not exceed 30 volumes, especially it is 25 volume equivalents or less, 20 volume equivalents or less or even 15 volume equivalents or less. In specific embodiments, the volume of the organic solvent in the reaction mixture is in the range of about 1% to about 200% of the volume of the surfactant-water mixture, in particular in the range of about 2% to about 150%, about 3% to about 120%, about 4% to about 110% or about 5% to about 100%.

In one embodiment, the reaction mixture is of industrial scale. It may for example have a volume of at least 1 l, in particular at least 10 l, at least 100 l, or at least 1000 l. In another embodiment, the reaction mixture is of microscale. It may for example have a volume of 10 ml or less, in particular 1 ml or less, 100 µl or less, 10 µl or less or 1 µl or less.

The reaction mixture is a charge or batch mixture for performing a chemical reaction. In certain embodiments the reaction mixture does not comprise any products of the reaction or comprises only residual amount of any products of the reaction. In other embodiments, it may also contain a significant amount of the product of the chemical reaction. In further embodiments, the reaction mixture does not comprise all reactants necessary to perform the chemical reaction. In particular, the reaction mixture comprises only one reactant. For example, in these embodiments one reactant may be added slowly to the reaction mixture and is directly consumed by the chemical reaction. In certain embodiments, the reaction mixture is a homogeneous mixture, especially a colloidal suspension. In particular, the reaction mixture does not contain aggregated or oiled out components such as reactant or product.

In a second aspect, the present invention provides a method of performing a chemical reaction, comprising the steps of

(a) providing a reaction mixture as described herein, and

(b) allowing the chemical reaction to proceed.

The reaction mixture especially comprises one or more reactants, a catalyst, and a surfactant-water mixture, wherein the catalyst is (a) a coupling reagent comprising one or more solubilizing groups; or (b) a metal ion in complex with a ligand comprising one or more solubilizing groups; wherein the solubilizing group comprises a C5-50 alkyl group or a poly(alkylene glycol) group with 2 to 20 repeating units. The reaction mixture in particular may exhibit any of the features, embodiments and examples described herein including combinations thereof.

The chemical reaction may be any chemical reactions which can be performed in a medium comprising a surfactant-water mixture. In particular organic chemical synthesis reactions can be performed, for example with at least partly hydrophobic compounds. Exemplary chemical reactions include chemical reactions selected from the group consisting of cross-coupling reactions such as Suzuki cross-coupling, Suzuki-Miyaura cross-coupling, Sonogashira cross-coupling, Heck cross-coupling, Buchwald-Hartwig cross-coupling, Negishi cross-coupling, Stille cross-coupling, Miyaura borylation, Hiyama cross-couplings, and olefin metathesis; copper-mediated cross-couplings, nickel-mediated cross-couplings, nucleophilic substitutions (S_N2) such as nucleophilic aromatic substitution (S_NAr); amidation; oxidation; reduction such as reduction of nitro groups, oxime groups, azide groups, nitrile groups and amide groups; hydrogenation and debenzylation. In certain embodiments, the chemical reaction is an amidation reaction. The reactants and the catalyst present in the reaction mixture are suitable for the specific chemical reaction. In particular, the reactants and the catalyst are specifically chosen so that the chemical reaction proceeds as desired.

In certain embodiments, the chemical reaction is allowed to proceed in step (b) at reaction conditions suitable for performing the chemical reaction. In particular, the reaction conditions include a temperature of 90°C or less, especially 80°C or less, 70°C or less, 60°C or less, 50°C or less, 40°C or less or 30°C or less. For example, the chemical reaction may be allowed to proceed at about room temperature. In specific embodiments, the reaction mixture is agitated, in particular stirred, during the course of the chemical reaction.

For some chemical reactions, the order and speed of the addition of the various components of the reaction mixture is important. In some embodiments, one or more of the reactants are added slowly to the surfactant-water mixture, optionally comprising further components of the reaction mixture such as other reactants, the catalyst and the base. This in particular applies to reactants which have a low solubility in water. Slow addition in this respect refers for example to the addition of the reactant over a time period of at least 5 min, in particular at least 7 min, at least 10 min, at least 15 min, at least 20 min, at least 30 min, at least 45 min or at least 60 min. A low solubility in water in particular refers to a water solubility of 20 g/l or less, especially 10 g/l or less or 5 g/l or less at room temperature. In these embodiments, an organic solvent may be added to the surfactant-water mixture before addition of the reactant or it may be added together with the reactant. For example, the reactant may be mixed with or solved in an organic solvent and then added to the surfactant-water mixture.

The methods of performing a chemical reaction may comprise the further step of isolating the product of the chemical reaction. In particular, this step is performed after completion of the chemical reaction. The product is in particular separated from one or

more, in particular essentially all of the other components of the reaction mixture. For example, the product is separated from one or more of remaining reactants, side products, catalysts, bases, organic solvents and/or surfactant-water mixture. Isolation of the product may be achieved by means and techniques known in the art, including for example evaporation of solvents, aggregation or crystallization and filtration, phase separation, chromatographic separation and others.

In certain embodiments, the reaction mixture is a homogeneous mixture throughout the entire chemical reaction, especially a colloidal suspension. "Throughout the entire chemical reaction" in this respect in particular means from the establishment of the final reaction mixture until the completion or termination of the chemical reaction.

The present invention improves the solubility of the reactants and products in the surfactant-water mixture and provides a stable and homogeneous reaction mixture. Thereby, the yield of the chemical reaction is increased and the amount of unwanted side products obtained by the chemical reaction is reduced. In view of this, the present invention in a further aspect provides a method of increasing the yield of a chemical reaction performed in a surfactant-water mixture, comprising the steps of

(a) providing a reaction mixture comprising one or more reactants, a catalyst, and a surfactant-water mixture, wherein the catalyst is a coupling reagent comprising one or more solubilizing groups, or a metal ion in complex with a ligand comprising one or more solubilizing groups; wherein the solubilizing group comprises a C_{5-50} alkyl group or a poly(alkylene glycol) group with 2 to 20 repeating units; and

(b) allowing the chemical reaction to proceed.

In a further aspect, the present invention provides a method of decreasing the amount of side products produced in a chemical reaction performed in a surfactant-water mixture, comprising the steps of

(a) providing a reaction mixture comprising one or more reactants, a catalyst, and a surfactant-water mixture, wherein the catalyst is a coupling reagent comprising one or more solubilizing groups, or a metal ion in complex with a ligand comprising one or more solubilizing groups; wherein the solubilizing group comprises a C_{5-50} alkyl group or a poly(alkylene glycol) group with 2 to 20 repeating units; and

(b) allowing the chemical reaction to proceed.

The embodiments, features and examples described herein, including combinations thereof, for methods of performing a chemical reaction and reaction mixtures likewise

apply to the method of increasing the yield of, and the method of decreasing the amount of side products produced in a chemical reaction performed in a surfactant-water mixture and the reaction mixture provided in step (a) thereof, respectively.

The reaction mixture may be provided in step (a) by adding the different components to each other in any suitable order. For example, providing the reaction mixture in step (a) may include providing a surfactant-water mixture and adding to said surfactant-water mixture a catalyst and one or more reactants.

The present invention also provides the use of a catalyst being

(a) a coupling reagent comprising one or more solubilizing groups; or

(b) a metal ion in complex with a ligand comprising one or more solubilizing groups;

wherein the solubilizing group comprises a C_{5-50} alkyl group or a poly(alkylene glycol) group with 2 to 20 repeating units; for increasing the yield of, and/or decreasing the amount of side products produced in a chemical reaction performed in a surfactant-water mixture.

The expression "comprise", as used herein, besides its literal meaning also includes and specifically refers to the expressions "consist essentially of" and "consist of". Thus, the expression "comprise" refers to embodiments wherein the subject-matter which "comprises" specifically listed elements may and/or indeed does encompass further elements as well as embodiments wherein the subject-matter which "comprises" specifically listed elements does not comprise further elements. Likewise, the expression "have" is to be understood as the expression "comprise", also including and specifically referring to the expressions "consist essentially of" and "consist of".

Numeric ranges described herein are inclusive of the numbers defining the range. The headings provided herein are not limitations of the various aspects or embodiments of this invention which can be read by reference to the specification as a whole. According to one embodiment, subject matter described herein as comprising certain steps in the case of methods or as comprising certain ingredients in the case of compositions refers to subject matter consisting of the respective steps or ingredients. It is preferred to select and combine specific aspects and embodiments described herein and the specific subject-matter arising from a respective combination of specific embodiments also belongs to the present disclosure.

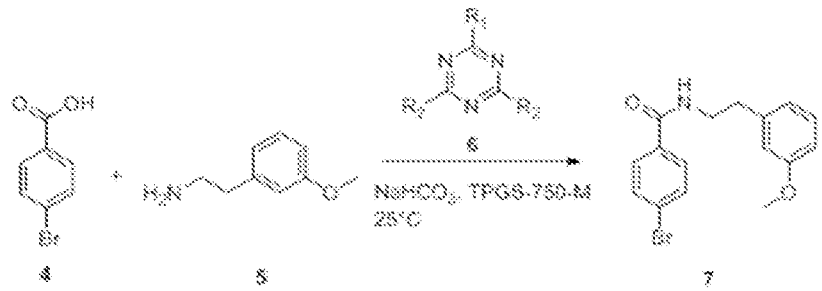
FIGURES

Figure 1 shows the chemoselective conversion of 4-bromobenzoic acid with 0.5 eq 3-methylphenol and 0.5 eq 3-ethylaniline using triazine 6c (A) or 6h (B) as coupling reagent in TPGS-750-M in water (2 wt%). In (A) the overall conversion (triangles) and the conversions into the amide (diamond) and the ester (circle) is shown. In (B) no conversion into the ester was observed, so that the conversion into the amide is identical to the overall conversion.

EXAMPLES

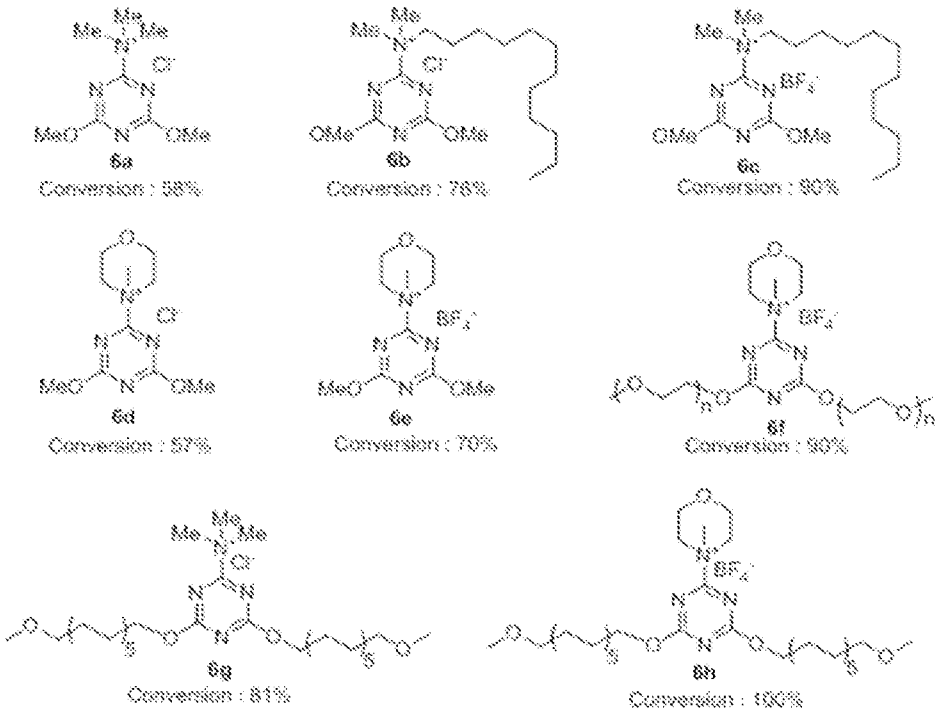
To a mixture of carboxylic acid (1 eq), $NaHCO_3$, (1 eq), and amine (1.1 eq) in TPGS-750-M (2% in water, 10 eq V) was added triazine (1.1 eq) in solution in a water-miscible co-solvent (1 eq V). The reaction was allowed to stir at 25°C until completion (typically 2 to 5 hours). At completion, the product was either precipitated by the addition of more water, or extracted in isopropyl acetate, and filtered through a short plug of silica to provide the desired amide product.

A variety of derivatized triazines (6b to 6h) were compared with the reference one (6a) on the following challenging model transformation:



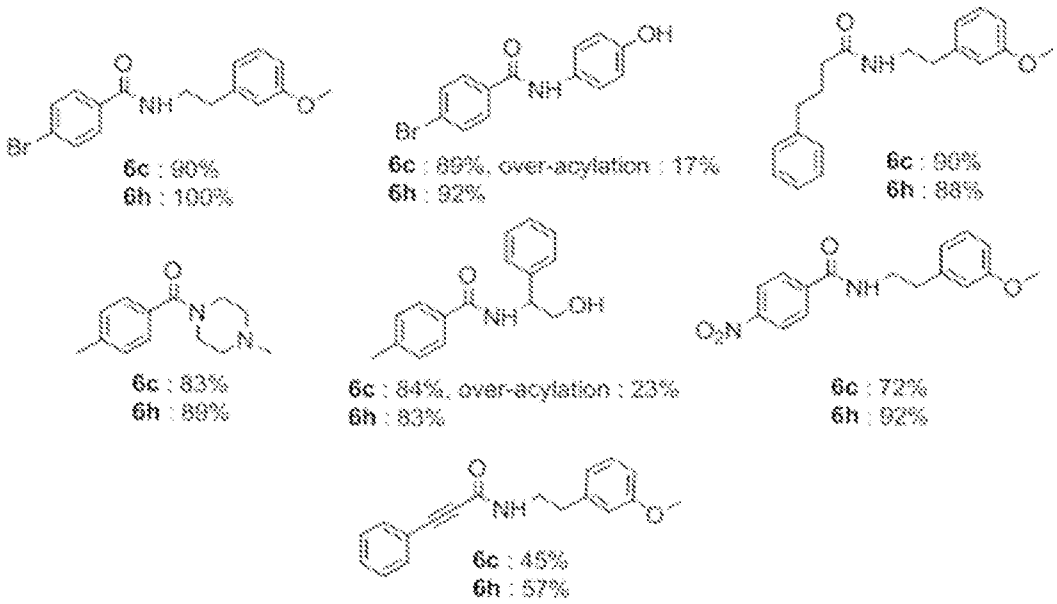
4 5 7

The following triazine derivatives were evaluated, giving the indicated conversion ratio:



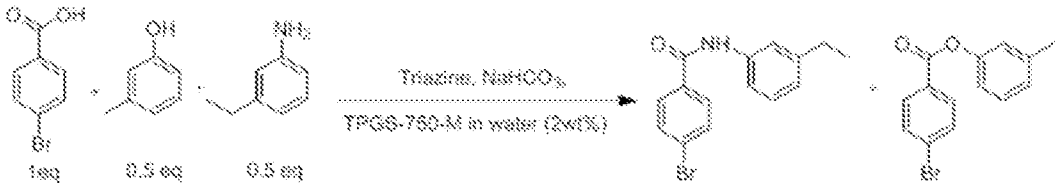
The conversions were monitored as a direct indicator of the yield (no competitive side-reaction). This demonstrated that tailoring the reagent for the medium had a profound impact on its outcome.

Amidation was then performed with different amines and carboxylic acids using the coupling reagent 6c or 6h, respectively. Conversion ratios were as follows:



We demonstrated here that the non-participating side-chains had the most profound impact, and always showed as good or better selectivity and yield.

Another and even more spectacular feature is the selectivity that ensues. On the highly demanding reaction below, triazine 6c or 6h, respectively, was used as coupling reagent and the formation of amide and ester was monitored.



The results are shown in figure 1. As can be seen, saw almost perfect selectivity was obtained in the case of triazine 6h (Figure 1B). This is all the more remarkable as it is almost impossible to obtain with any other conditions. Also with triazine 6c, only a very small amount of ester was obtained (Figure 1A).

CLAIMS

1. A reaction mixture comprising one or more reactants, a catalyst and a surfactant-water mixture, wherein the catalyst is

   (a) a coupling reagent comprising one or more solubilizing groups; or

   (b) a metal ion in complex with a ligand comprising one or more solubilizing groups;

   wherein the solubilizing group comprises a C_{5-50} alkyl group or a poly(alkylene glycol) group with 2 to 20 repeating units.

2. The reaction mixture according to claim 1, wherein the solubilizing group comprises a C_{5-50} alkyl group and has one or more of the following features:

   (i) the alkyl group is linear;

   (ii) the alkyl group comprises 8-15 carbon atoms, in particular 10-14 carbon atoms, especially 12 carbon atoms;

   (iii) it is substituted with one or more groups selected from methoxy, ethoxy, propoxy, hydroxy, amino optionally substituted with one or two of methyl, ethyl and/or propyl, in particular methoxy, ethoxy or hydroxy;

   (iv) it is 12-methoxydodecyl or dodecyl.

3. The reaction mixture according to claim 1, wherein the solubilizing group comprises a poly(alkylene glycol) group with 2 to 20 repeating units and has one or more of the following features:

   (i) the poly(alkylene glycol) group is a poly(ethylene glycol) group or poly(propylene glycol) group, in particular a poly(ethylene glycol) group;

   (ii) the poly(alkylene glycol) group has 3 to 8 repeating units, in particular 4 to 6 repeating units;

   (iii) it is substituted with one or more groups selected from methyl, ethyl, propyl, methoxy, ethoxy, propoxy, hydroxy, amino optionally substituted with one or two of methyl, ethyl and/or propyl, in particular methyl, ethyl or propyl;

   (iv) it is a poly(ethylene glycol) group with 4 to 6 repeating units, optionally substituted with methyl or ethyl at the terminal oxygen.

4. The reaction mixture according to any one of claims 1 to 3, wherein the solubilizing group is attached to the remaining part of the coupling reagent or ligand via an ether, amine, ester or amide bond.

5. The reaction mixture according to any one of claims 1 to 4, wherein the coupling reagent or ligand comprises one or two solubilizing groups.

6. The reaction mixture according to any one of claims 1 to 5, wherein the catalyst is a coupling reagent which is a 1,3,5-triazine derivative which optionally has one or more of the following features:

   (i) it comprises a quaternary amine, in particular attached to the 2-position of the triazine ring, which preferably is a trimethylamino or N-methyl-N-morpholino group;

   (ii) it is substituted with methyl, ethyl, propyl, methoxy, ethoxy and/or propoxy at the 4- and/or the 6-position of the triazine ring;

   (iii) the solubilizing group is attached to the quaternary amine and/or the 4- and/or 6-position of the triazine ring

7. The reaction mixture according to any one of claims 1 to 5, wherein the catalyst is a metal ion in complex with a ligand which is selected from the group consisting of a biphenyl compound, an N-heterocyclic carbene compound and a bipyridine compound.

8. The reaction mixture according to any one of claims 1 to 7, wherein the metal ion of the catalyst is selected from the group consisting of copper ion, ruthenium ion, rhodium ion, palladium ion, nickel ion, zinc ion, gold ion, manganese ion, iron ion and cobalt ion.

9. The reaction mixture according to any one of claims 1 to 8, wherein the surfactant is a non-ionic surfactant comprising a hydrophilic part and a hydrophobic part, wherein preferably the hydrophilic part of the surfactant comprises a polyethylene glycol moiety.

10. The reaction mixture according to any one of claims 1 to 9, wherein the surfactant is selected from the group consisting of (DL-α-) tocopherol polyethylene glycol succinate (TPGS) such as TPGS-750-M, TPGS-1000 and TPGS-1500; Triton X-100, polyethylene glycol alkyl ether such as Brij, polyethylene glycol ester such as polyethylene glycol (15)-hydroxystearate (Solutol HS 15), Tween such as Tween 20 or Tween 80, sodium dodecyl sulfate (SDS), cetyltrimethylammonium bromide (CTAB), phase transfer surfactants (PTS) (e.g. sodium deoxycholate),

polyoxyethanyl ubiquinol sebacate (PQS) and functionalized PQS, polyethylene glycol (PEG) and various derivatives such as C4-azo-PEG, octanoic acid and other long alkyl chain acids, and b-sitosterol methoxyethyleneglycol succinate (Nok).

11. The reaction mixture according to any one of claims 1 to 10, wherein the concentration of the surfactant in the surfactant-water mixture is 0.5 to 5% (w/w).

12. The reaction mixture according to any one of claims 1 to 11, wherein the reaction mixture comprising one reactant or two reactants.

13. The reaction mixture according to any one of claims 1 to 12, further comprising an organic solvent.

14. The reaction mixture according to any one of claims 1 to 13, wherein the reaction mixture is a homogeneous mixture.

15. The reaction mixture according to any one of claims 1 to 14, wherein the reaction mixture is a colloidal suspension.

16. A method of performing a chemical reaction, comprising the steps of

    (a) providing a reaction mixture according to any one of claims 1 to 15, and

    (b) allowing the chemical reaction to proceed.

17. The method according to claim 16, further comprising the step of isolating the product of the chemical reaction.

18. The method according to claim 16 or 17, wherein the reaction mixture is a homogeneous mixture throughout the entire chemical reaction.

19. The method according to any one of claims 16 to 18, wherein the reaction mixture is a colloidal suspension throughout the entire chemical reaction.

20. A method of increasing the yield of a chemical reaction performed in a surfactant-water mixture, comprising the steps of

    (a) providing a reaction mixture comprising one or more reactants, a catalyst, and a surfactant-water mixture, wherein the catalyst is a coupling reagent comprising one or more solubilizing groups, or a metal ion in complex with a ligand comprising one or more solubilizing groups; wherein the solubilizing group comprises a C_{5-50} alkyl group or a poly(alkylene glycol) group with 2 to 20 repeating units; and

(b) allowing the chemical reaction to proceed.

21. A method of decreasing the amount of side products produced in a chemical reaction performed in a surfactant-water mixture, comprising the steps of

(a) providing a reaction mixture comprising one or more reactants, a catalyst, and a surfactant-water mixture, wherein the catalyst is a coupling reagent comprising one or more solubilizing groups, or a metal ion in complex with a ligand comprising one or more solubilizing groups; wherein the solubilizing group comprises a C_{5-50} alkyl group or a poly(alkylene glycol) group with 2 to 20 repeating units; and

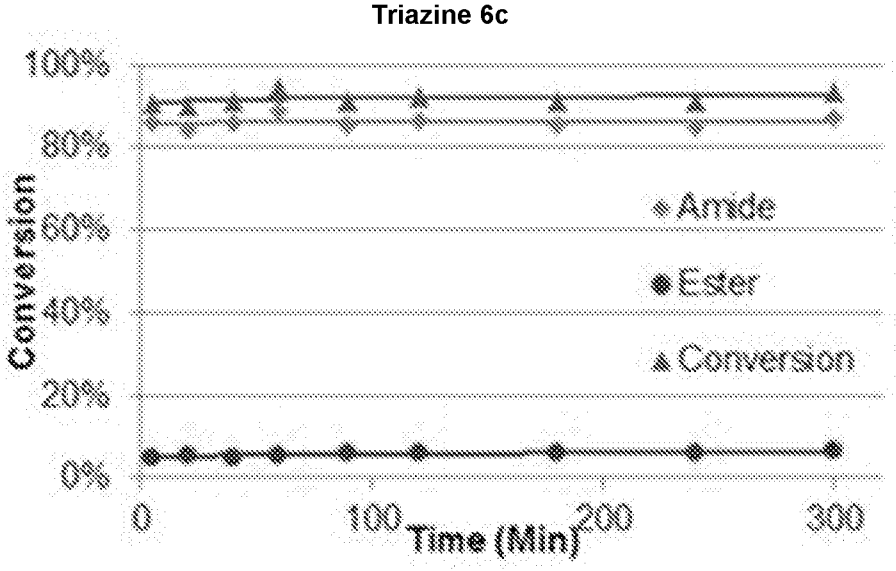
(b) allowing the chemical reaction to proceed.

22. The method according to claim 20 or 21, wherein the reaction mixture is a reaction mixture as defined in any one of claims 1 to 15.

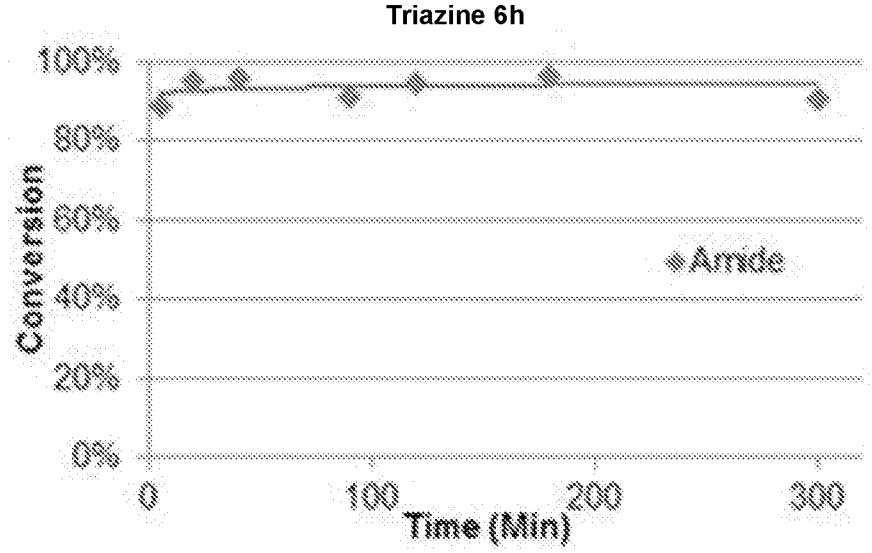
23. The method according to claim 20 or 21, comprising the method of performing a chemical reaction according to any one of claims 16 to 19.

Figure 1

A


Triazine 6c
100%
80%
60%
40%
20%
0%
Conversion
Amide
Ester
Conversion
0
100
200
300
Time (Min)

B


Triazine 6h
100%
80%
60%
40%
20%
0%
Conversion
Amide
0
100
200
300
Time (Min)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/054139

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01J31/02 B01J31/18 B01J31/22 B01J31/24 C07C231/02
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B01J C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LINDSTROEM U M: "STEREOSELECTIVE ORGANIC REACTIONS IN WATER", CHEMICAL REV, AMERICAN CHEMICAL SOCIETY, US, vol. 102, 1 January 2002 (2002-01-01), pages 2751-2772, XP008043682, ISSN: 0009-2665, DOI: 10.1021/CR010122P	3
A	page 2757; figure 3; compounds 12,13 page 2753	1,2,4-6, 9-14, 16-18, 20-23

-/--

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2017	12/12/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Goebel, Matthias

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LIU ET AL: "Toward green catalytic synthesis-Transition metal-catalyzed reactions in non-conventional media", JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL, ELSEVIER, AMSTERDAM, NL, vol. 270, no. 1-2, 7 May 2007 (2007-05-07) , pages 1-43, XP022044418, ISSN: 1381-1169, DOI: 10.1016/J.MOLCATA.2007.01.003	3
A	Scheme 20; page 14, right-hand column, paragraph 3 - page 15, right-hand column, paragraph 1; compounds 23-27 page 9, left-hand column, paragraph 3; compound 4	1,2,4-6, 9-14, 16-18, 20-23

Y	LIPSHUTZ B H ET AL: "PQS-2: ring-closing- and cross-metathesis reactions on lipophilic substrates; in water only at room temperature, with in-flask catalyst recycling", TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 66, no. 5, 30 January 2010 (2010-01-30), pages 1057-1063, XP026825868, ISSN: 0040-4020 [retrieved on 2009-11-06]	3
A	figure 2 Scheme 3; compound 3	1,2,4-6, 9-14, 16-18, 20-23

X	MUNETAKA KUNISHIMA ET AL: "Substrate-Selective Dehydrocondensation at the Interface of Micelles and Emulsions of Common Surfactants", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, vol. 51, no. 9, 20 January 2012 (2012-01-20), pages 2080-2083, XP055430616, ISSN: 1433-7851, DOI: 10.1002/anie.201107706	1-6, 9-14, 16-18, 20-23
Y	the whole document page 2082, right-hand column, paragraph 2; tables 1,2,3	2,4,5

	-/--	

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MUNETAKA KUNISHIMA ET AL: "Unusual Rate Enhancement of Bimolecular Dehydrocondensation To Form Amides at the Interface of Micelles of Fatty Acid Salts", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, vol. 44, no. 44, 17 October 2005 (2005-10-17), pages 7254-7257, XP055430648, ISSN: 1433-7851, DOI: 10.1002/anie.200502594	1,2,4-6, 9-14, 16-18, 20-23
Y	Scheme 1; page 7257; tables 1,2,3; compound 3	2-5
X	FABRICE GALLOU ET AL: "A General and Practical Alternative to Polar Aprotic Solvents Exemplified on an Amide Bond Formation", ORGANIC PROCESS RESEARCH AND DEVELOPMENT, vol. 20, no. 7, 22 June 2016 (2016-06-22), pages 1388-1391, XP055430499, US ISSN: 1083-6160, DOI: 10.1021/acs.oprd.6b00190	1,6, 9-14, 16-18, 20-23
Y	page 1388, right-hand column, paragraph 2 Scheme 1; page 1389, paragraph 5 - page 1390, paragraph 1; tables 1,2,3	2,4,5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/054139

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-6, 9-14, 16-18, 20-23(all partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-6, 9-14, 16-18, 20-23(all partially)

1. Claim 1 relates to an extremely large number of possible compositions, drafted mainly in vague functional and partly relative terminology ("coupling reagent" - how is what coupled?; "solubilizing groups" (hereinafter "SG") - to which extent, in which solvent?; "catalyst" - per se is only a designation of intended use; ditto "reactant(s)"). The only clear features are the broad terms "surfactant", "metal" and "ligand"; the definitions "alkyl" and "poly(alkylene glycol)" as such **would** be clear, but according to the description have further realizations not provided by their ordinary (IUPAC-) meanings (cf pages 9, line 28 - 10, line 17). Likewise the worked examples contain triazine AMIDE coupling agents, which are definitely outside the SG definition of claim 1 (compounds 6a, 6d, 6e: only methyl = C1 alkyl groups) and one compound **possibly** outside (6f, missing the value for index "n", i.e. #EO units); whereas compounds 6g and 6h would only fall within claim 1 **if** the further said substitution definitions of page 10 apply. Throughout the whole description, there is not a single further "chemical reaction" given together with concrete metal-ligand complexes, leaving thus the catalyst alternative (b) of claim 1 completely *undefined* as to its limitations, as well as to concrete realizations thereof. Thus separate choices for ligands, metals would need to be made to arrive at complexes, but no pointers are given; neither as to which of the heap of reactions given any such possible combination might apply to (pg 3, ll 13-25). Likewise, the functional statements on pages 4/5, bridging para. appear quite useless in this context, since absolutely no specific uses beyond "catalyst" are disclosed, hence metal catalyst (b) is effectively undefined from a functional point of view as well ("choice of catalyst depends on type of chemical reaction to be performed", page 5, lines 2-4). The skilled person would hence need to embark on an essentially unlimited research programme to (i) find the limits of claim 1, (ii) make its multitudinous conceivable embodiments work.

1.1 Support, a clear definition of subject-matter and disclosure within the meaning of Articles 5 and 6 PCT are to be found for only a *very small* proportion of the compositions claimed (see worked examples on pp 17-19 and pg 5, ll 5-6, as well as pp 5, lg 22 - 6, lg 22, tog. with pp 3, lg 31 - 4, lg 34).

1.2 Non-compliance with the substantive provisions is such that a meaningful search of the whole claimed subject-matter of claim 1 cannot be carried out (PCT Guidelines 9.19).

2. Since they all ultimately refer to the composition of claim 1, the same applies to the methods of claims 16, 20 and 21, mutatis mutandis.

Likewise, non-compliance with the substantive provisions is such that a meaningful search of the whole claimed subject-matter of claim 19 cannot be carried out (PCT Guidelines 9.19).

3 With respect to dependent claims 7, 8, these are related to said undisclosed metal complexes (b) of claim 1; colloidal systems are likewise not disclosed, as defined in dependent

claims 15 and 19, especially not for the disclosed AMIDE coupling reagent.

Non-compliance with the substantive provisions is such that a meaningful search of the claimed subject-matter of claims 7, 8, 15 and 19 cannot be carried out *at all* (Art. 17(2)(b) PCT).

4. Thus, pursuant to PCT Guidelines 9.19 and 9.24, the search was restricted to claims 1-6, 9-14, 16-18 and 20-23 and therein to those claimed compositions which at present appear to be supported and to a reasonable generalisation thereof.

In view of the many clarity, support and/or disclosure deficiencies in the present claims, these appear to be those of the worked examples on pages 17-19 and a reasonable generalisation thereof, as expressed by the subject-matter of:

- claims 1/16/20/21 *only* relating to AMIDE coupling reagents as catalysts, being sym-triazines as defined in claim 6, but further limited as on pages 5, line 22 - 6, line 22, with alkyl and PAG groups having the further substitution options of pages 9, line 28 - 10, line 17, further with the respective preferred options in the combination of the preferred options (i)+(ii) in claim 6 forming another alternative embodiment of AMIDE coupling reagent (= worked examples, compounds 6a, 6d, 6e), together with reactants= carboxylic acid and amine for amide formation, as well as surfactants as defined on pages 3, line 31 - 4, line 34;
- the dependent claims being adapted accordingly.

5. Notwithstanding the above, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty, incl. common household items like laundry detergent, comprising enzymes (metal ions with solubilizing ligands, e.g. (iso)leucin or lysine side-chains), surfactants, the enzymes being the catalysts to remove organic stains (= reactant(s)).

A search incl. such clearly known compounds is *not meaningful*, too many documents would be retrieved, obscuring any subject-matter for which protection might legitimately be sought (Art 6 PCT).

A small selection is given in D1-D3.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.