

CATALYST IMMOBILIZATION ON SILICEOUS MESOCELLULAR FOAM VIA CLICK CHEMISTRY

CROSS REFERENCE TO RELATED APPLICATION

This application claims benefit of, and priority from, U.S.
5 provisional patent application No. 60/907,134, filed on
March 22, 2007, the contents of which are fully incorporated
herein by reference.

FIELD OF THE INVENTION

This invention relates to the application of "click
10 chemistry" for the immobilisation of catalysts on siliceous
mesocellular foams (MCF).

BACKGROUND OF THE INVENTION

Sharpless and co-workers first introduced the concept of
"click chemistry",^[1] employing powerful and selective
15 reactions for the efficient synthesis of interesting
compounds and materials through heteroaromatic links, e.g.,
Huisgen 1,3-dipolar cycloaddition of azides and alkynes.^[2]
This modular process is reliable, widely applicable, of high
yield, and requires only simple reaction and purification
20 conditions. It does not involve reagents that are difficult
to handle, and is stable towards strong bases.^[3]

Recently, applications of "click chemistry" were reported in
the synthesis of chemically and biologically useful
materials.^[4,5] However, the development of heterogenized
25 catalysts has seemingly produced the most significant impact
on the chemical and pharmaceutical industries.^[6,7] Although
attempts to immobilise homogeneous catalytic complexes (not
via click chemistry) on various supports have been
reported^[7A], these have not always generated sufficiently
30 effective heterogenized catalysts for industrial

applications. Immobilised catalysts (also referred to herein as heterogenised catalysts) can offer a number of advantages, such as ease of catalyst recovery and products isolation, reduced production costs, and decreased catalyst contamination of products, etc.^[8,9] Such systems are of great interest given the growing demands of inexpensive green chemistry.^[32]

BRIEF SUMMARY OF THE INVENTION

In one aspect, the present invention provides a method for preparing a heterogenised catalyst, comprising grafting a catalyst or catalyst precursor, via click chemistry, to a siliceous mesocellular foam (MCF).

In another aspect, the present invention provides a heterogenised catalyst comprising a catalyst species grafted onto a siliceous mesocellular foam (MCF) via a 1,2,3-triazole.

The above and other features and advantages of the present invention will become apparent from the following description when taken in conjunction with the accompanying figures which illustrate preferred embodiments of the present invention by way of example.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the invention will be discussed with reference to the following Figure:

Figure 1 displays the structures of four heterogenised organocatalysts.

DETAILED DESCRIPTION OF THE INVENTION

Click chemistry has been adopted for the immobilisation of several types of compounds on different supports, including

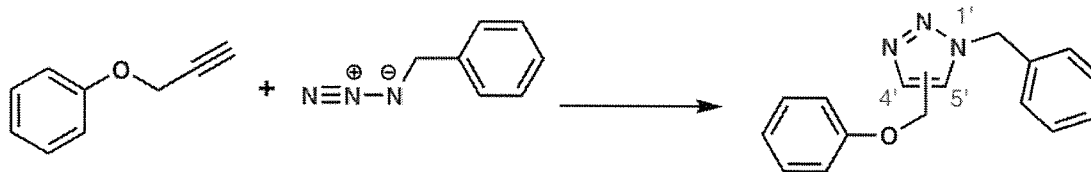
silica. However, the beneficial combination of click chemistry and siliceous mesocellular foam (MCF) has not been explored previously for the development of heterogenised catalysts with high cost efficiency, environmental compatibility, and catalytic activity. The present invention provides a facile and inexpensive method for the preparation of efficient and reusable catalyst systems, which method is widely applicable to a variety of ligands, catalysts, solvents, and supports. The MCF microparticles can also be easily tailored in terms of microstructure, pore size and surface chemistry for specific applications.

Click chemistry

Click chemistry is a chemical philosophy that describes chemistry tailored to generate substances quickly and reliably by joining small units together. Generally, click chemistry encourages reactions that have modular applications that are wide in scope, that have a high chemical yield, that generate inoffensive by-products, that are stereospecific, that require simple reaction conditions, that use readily available starting materials and reagents, that are solvent free or use benign solvents such as water, that lead to easy product isolation by crystallisation or distillation but not preparative chromatography, that have a large thermodynamic driving force to favour a reaction with a single reaction product, and that have a high atom economy. While certain of the general criteria can be subjective in nature, and not all criteria need to be met, several reactions are generally recognised as "click chemistry" reactions. Examples of such include the Huisgen 1,3-dipolar cycloaddition and variants thereof.

The azide-alkyne Huisgen cycloaddition is a 1,3-dipolar cycloaddition between an azide and a terminal or internal

alkyne to give a 1,2,3-triazole. This reaction can be exemplified as follows:



In the reaction above the azide reacts with the alkyne to afford the triazole as a mixture of 1,4-adduct and 1,5-adduct.

A notable variant of the Huisgen 1,3-dipolar cycloaddition is the copper(I) catalysed variant, in which organic azides and terminal alkynes are united to afford 1,4-regioisomers of 1,2,3-triazoles as sole products. The reaction can be performed using commercial sources of copper(I), such as cuprous bromide or iodide, or with other copper sources such as a mixture of copper(II) (e.g. copper(II) sulfate) and a reducing agent (e.g. sodium ascorbate) to produce Cu(I) in situ. As Cu(I) is unstable in aqueous solvents, stabilising ligands, such as tris-(benzyltriazolylmethyl)amine (TBTA), can be used. The reaction can be carried out in a variety of solvents, examples of which include mixtures of water with a variety of miscible or partially miscible organic solvents such as alcohols, DMSO, DMF, tBuOH and acetone.

In one embodiment of the above reactions, the terminal alkyne can be protected with a trimethyl silyl protecting group, followed and subsequent deprotection after the radical reactions are complete.

25 Siliceous mesocellular foam

Siliceous MCF microparticles serve as an excellent support material, and click chemistry provides a highly reliable and

widely applicable tool for the grafting of catalytic complexes.

Siliceous mesocellular foam (MCF)^[10] has been found to be a very useful support material for heterogenised catalysts.^[11]

5 The physical and chemical robustness of MCF allow this material to be easily handled both at the laboratory and manufacturing scales. These foams facilitate reactions involving bulky substrates without diffusion limitations, and can be used to host large catalytic complexes without
10 steric hindrance.^[12] Hence, it is advantageous to use this mesoporous silica material as a solid support in combination with click chemistry to develop novel heterogenized catalysts.^[13,14]

Siliceous mesocellular foams can be prepared according to
15 known methods, such as those taught in international publication No. WO/2006/135339, the contents of which are incorporated herein by reference.

The foam may comprise cell-like mesopores connected by windows of a smaller size. The mean pore size (e.g. cell
20 pore size) may be greater than about 5nm, or greater than about 10nm. It may be between about 5 and about 100nm or between about 5 and 50, 5 and 20, 10 and 30, 50 and 100, 20 and 30, 20 and 25, 2 and 22, 24 and 42, 25 and 30, 27 and 30, 27 and 29, or 10 and 50nm. The pore size may be about 5,
25 10, 15, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100nm. The ratio of the size of the mesopores and the size of the windows may be between about 10:1 and about 1.5:1, or between about 10:1 and 2:1, 10:1 and 5:1, 5:1 and 1.5:1, 3:1
30 and 1.5:1, 5:1 and 3:1 or 8:1 and 4:1, and may be about 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4.5:1, 4:1, 3.5:1, 3:1, 2.5:1, 2:1 or 1.5:1, or may be some other ratio. The size of the windows (i.e. window pore size) may be greater than

about 2nm, greater than 5nm, or greater than about 10nm. It may be between about 2 and about 100nm or between about 2 and 50, 2 and 10, 5 and 50, 5 and 20, 10 and 20, 10 and 15, 10 and 12, 15 and 20, 15 and 18, 15 and 17, 10 and 100, 50 and 100 or 10 and 50nm. The window size may be about 2, 3, 4, 5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60 65, 70, 75, 80, 85, 90, 95 or 100nm. The particles may have a distribution of different window sizes. The different window sizes may be between about 2 and 100nm. In one embodiment, the mean pore size is between 24 and 42nm and the windows connecting the pores have a diameter from 9 to 22nm.

The particles of regular shaped solid foam may have a mean particle diameter of between about 1 and about 20 microns, or between about 2 and about 50, 20 and 50, 10 and 50, 2 and 40, 1 and 10, 1 and 5, 1 and 2, 2 and 20, 2 and 10, 3 and 8, 4 and 7, 4 and 6, 5 and 20, 10 and 20, 2 and 10 or 5 and 10 microns, and may have a mean particle diameter of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19- 20, 25, 30, 35, 40, 45 or 50 microns, or may be less than 1 micron or greater than 50 microns. The particles of solid foam may have a narrow particle size distribution or the particles may have a distribution of different pore sizes. There may be less than about 50% of particles having a particle size more than 10% different from (greater than or less than) the mean particle size, or there may be less than about 45, 40, 35, 30, 25, 20, 15, 10 or 5% of particles having a particle size more than 10% different from the mean particle size, and may be about 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50% of particles having a particle size more than 10% different from the mean particle size.

The particles may have a pore volume of between about 0.5 and about 5 cm³/g, or between about 0.5 and 4, 0.5 and 3, 0.5 and 2, 1 and 5, 2 and 5, 3 and 5, 1 and 3, 1 and 2, 2 and 3,

1.5 and 2, 1.5 and 1.7, 2 and 2.5, 2.2 and 2.4 or 2 and 2.4, and may have a pore volume about 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5 or 5cm³/g or more than about 5cm³/g. The particles may have a specific surface area of between about 100 and about 1000m²/g, or between about 100 and 500, 100 and 200, 200 and 1000, 500 and 1000, 200 and 800, 200 and 500, 500 and 800, 500 and 700, 500 and 600, 550 and 600, 550 and 570, 600 and 800, 650 and 750, 670 and 730 or 690 and 710 m²/g, and may have a specific surface area of about 100, 150, 200, 250, 300, 350, 400, 450, 500, 510, 520, 530 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 750, 750, 800, 850, 900 950 or 1000 m²/g, or may have a specific surface area of less than about 100 or greater than about 1000 m²/g.

The foam may comprise silica, aluminosilicate or silica doped with a metal such as aluminium, tin or lead. The foam may comprise mesoporous silica.

The particles of solid foam may be spherical, or they may be some other shape, such as ovoid, ellipsoid, cubic, rhomboidal, prismatic, or parallelepiped (for example rectangular parallelepiped). The particles may be hydrophilic or they may be hydrophobic. If they are hydrophobic, they may have alkyl groups (for example alkylsilyl groups) or aryl groups (for example from arylsilyl groups) on their surfaces. The alkyl groups may comprise C₁ to C₂₀ straight chain or branched alkyl groups, for example methyl, ethyl, octyl, octadecyl or isopropyl. The arylsilyl groups may comprise for example phenyl or tolyl groups. The particles of solid foam may have trimethylsilyl groups on their surfaces.

Method for obtaining heterogenised catalysts

The methods of the invention offer environmentally friendly and often less costly synthesis options for chemicals and pharmaceuticals. Further, heterogenised catalysts obtained
5 by the methods exhibit excellent activity and reusability, with tolerance to a range of substrates and reaction media.

The methods of the invention can be used to obtain a variety of heterogenised catalysts; both metal-based catalysts (i.e. organometallic catalysts) and non-metal catalysts (i.e.
10 organocatalysts).

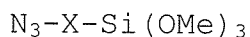
In one embodiment, heterogenised catalysts comprising one or more metal atoms are prepared by grafting, by click chemistry, a catalyst precursor such as a ligand (that bears or has been derivatised to bear a chemical group suitable
15 for click chemistry) to the siliceous MCF, and to then combine the immobilised ligand with the metal species, optionally together with further ligand molecules. In another embodiment, a fully or partially formed metal-comprising catalyst, which comprises a ligand having a
20 chemical group suitable for click chemistry, is grafted onto the siliceous MCF (optionally followed by further reactions to complete the catalyst species if a partially formed metal-bearing catalyst is grafted). In a further embodiment, a catalyst which does not contain a metal atom
25 (also referred to herein as an organocatalyst) can be derivatised such that it bears a chemical group suitable for click chemistry, and then grafted onto the siliceous MCF.

In one embodiment, the catalyst or catalyst precursor can be grafted to the siliceous MCF by way of a linker moiety. For
30 example, the linker moiety can bear an alkyne group or an azide group, along with a group that can react with the siliceous MCF. The linker can then be reacted with the

catalyst or catalyst precursor (which will bear an alkyne group or an azide group, as appropriate) by way of a 1,3-dipolar cycloaddition reaction to form an intermediate, which intermediate is then reacted with the siliceous MCF.

5 Alternatively, the linker moiety can be reacted to the siliceous MCF to form an intermediate, which intermediate is then reacted with the catalyst or catalyst precursor by way of a 1,3-dipolar cycloaddition reaction.

10 Examples of suitable linker moieties include molecules that comprise an azide or an alkyne group, together with a group that can react with the siliceous MCF. Examples of such groups include trialkoxy silyl groups, e.g. trimethoxy silyl. In one embodiment, the linker moiety can have the
15 formula :



wherein X is $\text{-CH}_2\text{CH}_2\text{-}$ or $\text{-C}_6\text{H}_4\text{-}$.

Any type of catalyst can be used in the present invention, as long as it comprises or can be derivatised to comprise a
20 chemical group suitable for click chemistry. Examples of suitable types of catalysts include ring-closing metathesis catalysts, cyclopropanation catalysts, and organocatalysts such as amino acids. Specific examples of suitable catalysts for use with the methods of the invention are
25 provided below.

EXAMPLES

The following examples are provided to illustrate the invention. It will be understood, however, that the specific details given in each example have been selected
30 for purpose of illustration and are not to be construed as limiting the scope of the invention. Generally, the

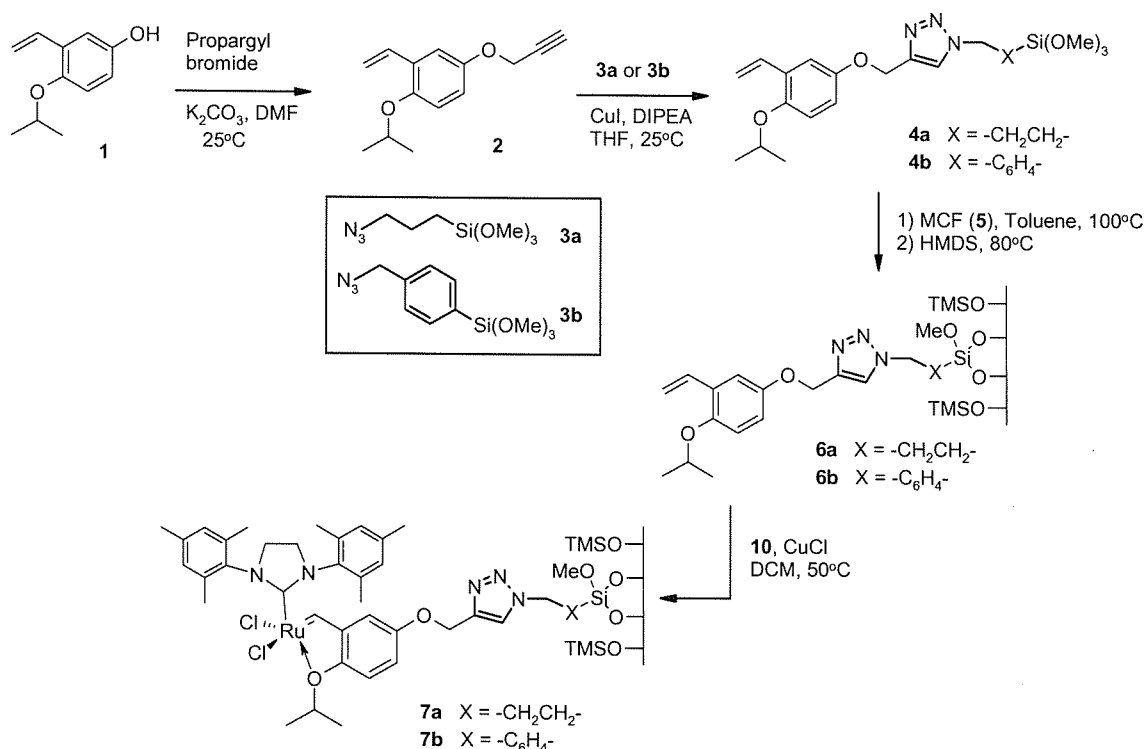
experiments were conducted under similar conditions unless noted.

Example 1: Ring-Closing Metathesis

Ring-closing metathesis (RCM) has played a key role in the generation of various cyclic motifs.^[15] However, the pharmaceutical industry has not yet widely utilized RCM in large-scale manufacturing due largely to the high cost of the ruthenium-containing compounds, and the significant metal leaching problem. For example, Ruthenium residue levels must be less than 5 ppm and 0.5 ppm for oral and parental drug products, according to the guidelines of European Agency for the Evaluation of Medicinal Products^[16]. Although many research groups have reported on the immobilization of the first- and second-generation Grubbs' catalysts on various supports,^[17] these heterogenized catalysts suffer from shortcomings such as low activity due to diffusion-related issues, reduced activity upon reuse, and requirement for further purification.^[18]

The preparation of immobilized ruthenium catalysts for RCM is depicted in Scheme 1.

Scheme 1



Alkyne **2** was readily prepared from the known phenol **1**^[18] by propargylation under mild conditions. Treatment of **2** with **3a/b** freshly prepared from the corresponding bromides produced the triazoles **4a/b** in the presence of Cu(I) iodide. The Hoveyda-Grubbs type ligands were smoothly grafted onto partially trimethylsilyl (TMS)-precapped MCF at 100°C in toluene to provide the immobilized ligands **6a/b**, whose structures were confirmed by photoacoustic Fourier-transform infrared (PA-FTIR) and cross-polarization magic angle spinning (CPMAS) ¹³C nuclear magnetic resonance (NMR) spectra.

The green powders were isolated by treating the commercially available second-generation Grubbs catalyst and the functionalized MCF **6a/b** in refluxing dichloromethane (DCM) in the presence of Cu(I) chloride,^[19] followed by filtration and drying. The incorporation of ruthenium onto the immobilized ligand **6a/b** was accomplished in good yields.

Table 1 summarizes the loading densities of ligand in **6a/b** and ruthenium in **7a/b**, respectively.

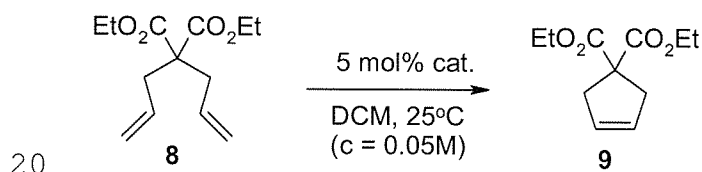
Table 1

Entry	Catalyst	Ligand in 6 ^[a] (mmol/g)	Ru in 7 ^[a] (mmol/g)	Ru/ligand ratio
1	7a	0.19	0.16	0.9
2	7b	0.19	0.16	0.9

^[a]Determined by elemental analysis.

- 5 These numbers could be easily controlled by the ratio of **4a/b** and Grubbs catalyst. The heterogenized ruthenium catalysts **7a/b** exhibited good activity and recyclability, and were stored for more than several months without activity loss.^[20]
- 10 The activity of heterogenized catalysts **7a/b** was tested for RCM by using diethyl diallylmalonate **8** as the benchmark substrate. The diene **8** was smoothly and completely transformed into the cyclised product **9** within 1.5 h by using 5 mol% of **7a/b** in DCM at ambient temperature without
- 15 forming noticeable side-products, as indicated by NMR spectroscopy (Table 2).

Table 2



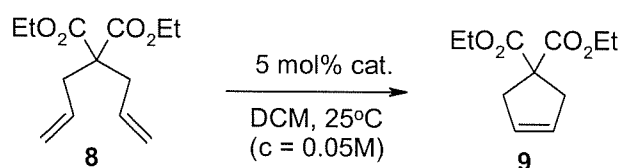
Entry	Catalyst	Conversion (%) ^[a]						
		0 h	0.25 h	0.50 h	0.75 h	1.00 h	1.25 h	1.50 h
1	7a	0	59	86	97	99	100	—
2	7b	0	44	78	88	97	99	100
3	10	0	84	98	99	100	—	—

^[a]Determined by gas chromatography (GC).

The immobilised catalysts **7a/b** proved to be less efficient than the commercially available second-generation Hoveyda-Grubbs catalyst (10). However, the reaction rate could be enhanced by tuning the linker moiety in **7a/b**. The more flexible propyl linker led to faster conversion, while the more rigid benzyl counterpart exhibited slower conversion. These differences were not significant, however.

Excellent recyclability of **7a/b** was demonstrated in Table 3, particularly at an elevated temperature associated with the reduced reaction time.

Table 3



Entry	Catalyst	Conditions	Conversion in each run (%) ^[b]				
			Run 1	Run 3	Run 5	Run 7	Run 10
1	7a	50°C, 0.5 h	99	96	94	91	91
2		25°C, 1.5 h	99	96	94	89	69
3	7b	50°C, 0.5 h	100	98	98	93	91
4		25°C, 1.5 h	100	95	94	88	78

These results correlated well to our previous results with the carbamate linkers.^[11e]

Example 2: Preparation of RCM Ligand 2

A Schlenk flask was charged with phenol **1** (10.0 mmol), propargyl bromide (12.0 mmol), potassium carbonate (12.0 mmol), and dried DMF (20 ml) under argon. The reaction mixture was stirred at 60°C for 12 h. Upon complete conversion of **1** by thin layer chromatography (TLC), the resulting mixture was cooled to room temperature and diluted with ethyl acetate (100 ml), washed with water (2 × 50 ml) and brine (50 ml) successively. The organic layer was dried over magnesium sulfate, and concentrated under reduced

pressure. A flash column chromatography (hexane:ethyl acetate = 4:1) gave alkyne **2** (8.20 mmol) as a colourless oil. ¹H-NMR (400 MHz, CDCl₃): δ 1.33 (d, 6H, *J* = 6.0 Hz), 2.54 (t, 1H, *J* = 1.8 Hz), 4.42 (septet, 1H, *J* = 6.0 Hz), 4.67 (d, 2H, *J* = 1.8 Hz), 5.26 (dd, 1H, *J* = 11.2, 1.2 Hz), 5.72 (dd, 1H, *J* = 17.6, 1.2 Hz), 6.85 (bs, 2H), 7.05 (dd, 1H, *J* = 17.6, 11.2 Hz), 7.13 (bs, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ 22.2, 55.5, 72.1, 75.4, 78.8, 112.7, 114.4, 115.2, 116.5, 129.2, 131.6, 150.1, 151.8.

10 **Example 3: Preparation of RCM Catalysts 7a and 7b**

Click Chemistry reaction

A Schlenk flask was charged with alkyne **2** (0.50 mmol), trimethoxysilane **3a** (0.50 mmol), Cu(I) iodide (5 μmol), and *N,N'*-diisopropylethylamine (DIPEA) (1.00 mmol) in THF (5 ml). The resulting mixture was stirred at ambient temperature for 12 h under argon. The volatile components were completely removed under reduced pressure to give the triazole **4a** as a colourless oil in a quantitative yield, which was used for the next step without further purification. ¹H-NMR (400 MHz, CDCl₃): δ 0.61-0.65 (m, 2H), 1.32 (d, *J* = 6.0 Hz, 6H), 2.04 (quintet, 2H, *J* = 7.6 Hz), 3.57 (s, 9H), 4.37 (t, *J* = 7.6 Hz, 2H), 4.40 (septet, *J* = 6.0 Hz, 1H), 5.20 (s, 2H), 5.25 (dd, 1H, *J* = 11.2, 1.2 Hz), 5.72 (dd, 1H, *J* = 17.6, 1.2 Hz), 6.85 (bs, 2H), 7.04 (dd, 1H, *J* = 17.6, 11.2 Hz), 7.14 (d, 1H, *J* = 2.4 Hz), 7.62 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ 6.2, 22.2, 24.0, 50.7, 52.5, 62.7, 72.1, 112.5, 114.4, 114.9, 116.7, 122.6, 129.3, 131.6, 144.3, 149.8, 152.5. MS (FAB): *m/z* (%) 422 (100) [M⁺+H], 453 (10), 268 (14).

The general procedure for click chemistry using **2** (0.50 mmol) and **3b** (0.50 mmol) gave **4b**. ¹H-NMR (400 MHz, CDCl₃): δ 1.32 (d, *J* = 6.0 Hz, 6H), 3.63 (s, 9H), 4.40 (septet, *J* =

6.0 Hz, 1H), 5.18 (s, 2H), 5.25 (dd, 1H, $J = 11.2, 1.2$ Hz), 5.56 (s, 2H), 5.69 (dd, 1H, $J = 17.6, 1.2$ Hz), 6.83 (bs, 2H), 7.03 (dd, 1H, $J = 17.6, 11.2$ Hz), 7.11 (bs, 1H), 7.31 (d, 2H, $J = 7.6$ Hz), 7.67 (d, 2H, 7.6 Hz). ^{13}C -NMR (100 MHz, CDCl_3): δ 22.2, 50.9, 54.1, 62.7, 72.1, 112.6, 114.4, 114.9, 116.6, 122.6, 127.5, 129.3, 130.4, 131.6, 135.6, 136.8, 145.0, 149.9, 152.4. MS (FAB): m/z (%) 470 (100) [M^+H], 264 (10), 211 (73). HRMS (FAB) calculated for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_5\text{Si}$: 470.2106 [M^+H], found 470.2098.

10 Ligand Grafting

A Schlenk flask was charged with the TMS-precapped MCF **5** (2.00 g, 0.60 mmol TMS/g), and placed under vacuum for 24 h at 120°C. The flask was purged with argon at room temperature, and charged with dried toluene (40 ml) and trimethoxysilane **4a** (0.50 mmol). The resulting mixture was heated for 24 h at 90°C. Upon cooling to room temperature, the solid was thoroughly rinsed by toluene, DCM, methanol, and DCM (50 ml each). The white solid was transferred to a Schlenk flask, and dried under vacuum for 12 h at 80°C. After cooling down to room temperature, the flask was placed in liquid nitrogen bath for 10 min, and HMDS (1 ml) was added at -200°C under vacuum. The flask was sealed, and then kept at 80°C for 5 h. The resulting solid was cooled to room temperature, washed thoroughly with DCM (100 ml), and then dried under vacuum for 24 h to give the immobilised ligand **6a** as a white powder. ^{13}C CP-MAS NMR: δ 3.64, 13.3, 23.8, 27.3, 54.5, 65.7, 74.5, 115.0, 119.5, 124.8, 132.9, 135.4, 147.8, 153.2, 156.5. Elemental analysis, found: C, 9.16; H, 1.90; N, 0.87. Loading of ligand: 0.19 mmol/g.

The general procedure for ligand grafting using **5** (2.00 g, 0.60 mmol TMS/g) and **4b** (0.50 mmol) gave **6b**. Elemental analysis, found: C, 9.98; H, 1.85; N, 0.85. Loading of ligand: 0.19 mmol/g.

Ruthenium Loading

A two-necked flask equipped with a reflux condenser was charged with ligand **6a** (2.00 g, 0.19 mmol/g), second-generation Grubbs' catalyst (0.38 mmol), copper chloride (0.38 mmol), and dried DCM (20 ml) under argon. The reaction mixture was heated for 5 h under reflux in argon. The reaction mixture gradually changed from dark brown to deep green. After cooling to room temperature, the fine powder was washed thoroughly with DCM (100 ml) under open atmosphere, and dried under vacuum for 24 h to give the immobilised catalyst **7a** as a green powder. Elemental analysis, found: C, 12.65; H, 2.15; N, 1.23. Loading of ruthenium: 0.16 mmol/g.

The general procedure for ruthenium loading using **6b** (2.00 g, 0.19 mmol/g) gave **7b**. Elemental analysis, found: C, 13.47; H, 2.13; N, 1.29. Loading of ruthenium: 0.16 mmol/g.

Testing Catalytic Activity for RCM

Reactions were run in a vial containing a magnetic stir bar in argon at room temperature. The vial was charged with catalysts **6a/b** (5 μ mol) and DCM (2 ml). The substrate **8** (0.10 mmol) was injected via a syringe. The conversions were monitored by GC after filtration through a short pad of silica gel by elution with DCM.

Testing Catalyst Recyclability for RCM

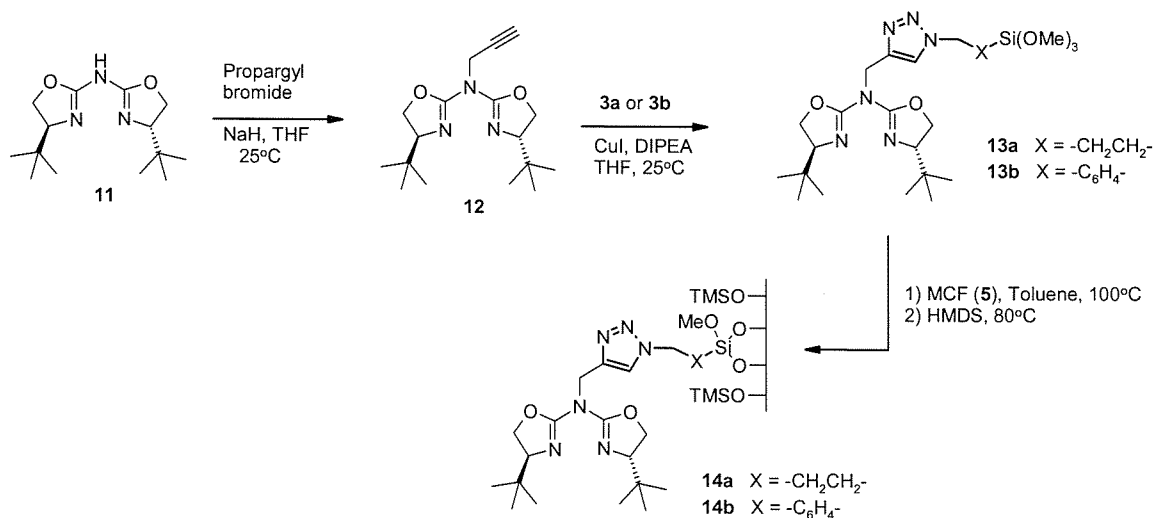
Reactions were run in a similar manner as described above. On completion of each run, the reaction vial was centrifuged at 4000 rpm for 3 min. The supernatant was characterised by GC for conversion. The vial was charged with another aliquot of DCM, stirred for 1 min, and centrifuged again. One more rinse was performed before the next run was conducted with fresh substrate.

Example 4: Cyclopropanation

Chiral bisoxazolines (BOX) have demonstrated high selectivity for various asymmetric catalytic reactions.^[21] However, the corresponding organometallic catalysts suffered from low turnover numbers (TON) in achieving the high enantioselectivity. Thus, there has been a great deal of interest to immobilise these catalysts on various supports.^[22,23] Click chemistry was adopted for immobilizing azabisoxazoline (azaBOX) onto MCF, not merely as a tool for combining two small molecules, but as a protocol for grafting.

The known amine **11**^[24] was readily prepared and reacted with propargyl bromide to give the alkyne **12**, mediated by sodium hydride in tetrahydrofuran (THF). This relatively unstable ligand was immediately "clicked" with **3a/b** in the presence of Cu(I) iodide to give the triazoles **13a/b** in quantitative yields, whose structures were elucidated by PA-FTIR and CPMAS ¹³C-NMR spectra (Scheme 2).

Scheme 2



The precursors **13a/b** were smoothly grafted at an elevated temperature in toluene onto TMS-precapped MCF (5). The preparation of the MCF-supported azaBOX **14a/b** was completed

by postcapping the remaining silanol via treatment with hexamethyldisilazane (HMDS) in vapor phase.

Starting from **11**, the overall yields of **14a/b** were over 70%.

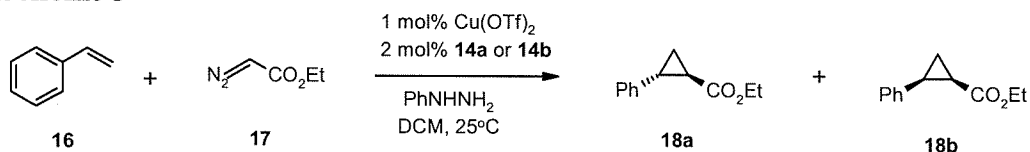
Introduction of metal was accomplished by adding Cu(II)

5 triflate into a THF suspension of **14a/b**. After stirring for 1 h, the suspension was filtered, washed with THF thoroughly, and dried under vacuum to produce the corresponding Cu(II) complexes (**15a/b**).

Cyclopropanation was performed over Cu(I) complexes, which

10 were generated in situ by reducing Cu(II) complexes with phenylhydrazine (PhNHNH₂) (Scheme 3).

Scheme 3



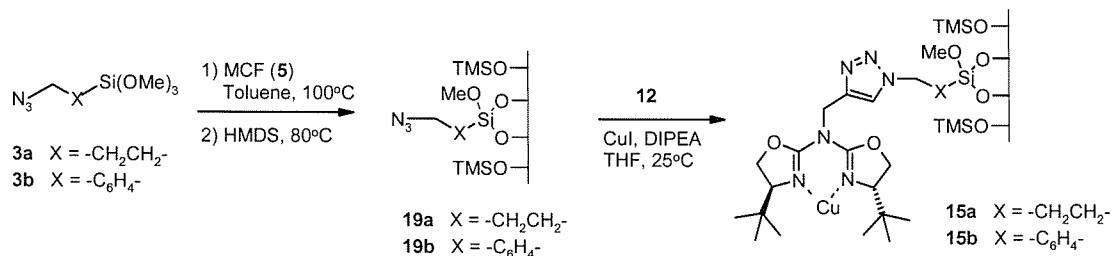
In the formation of cyclopropane **17a/b**, excellent

15 enantioselectivity and recyclability were achieved by utilising our immobilised Cu-azaBOX complexes.

A more facile synthesis of **15a/b** was examined by performing grafting and complexation in one pot using a stoichiometric amount of Cu(I). The immobilised azide **19a/b** was readily

20 prepared by condensation of **3a/b** and **5** in toluene, followed by postcapping with TMS group (Scheme 4).

Scheme 4



The complexes **15a/b** were smoothly formed by reacting **12** and

25 **19a/b** in the presence of > 0.5 equivalent of Cu(I) iodide in

THF. A tandem reaction of triazole formation and Cu(I) complexation significantly facilitated the preparation of azaBOX-based heterogenised catalysts for enantioselective cyclopropanation.

5 **Example 5: Preparation of BOX Ligand 12**

Amine **11** (10.0 mmol) in THF (10 ml) was added slowly at ambient temperature to a Schlenk flask charged with sodium hydride (12.0 mmol) as a suspension in THF (20 ml). The resulting mixture was stirred at 60°C for 1 h, and then
10 cooled to ambient temperature prior to the addition of propargyl bromide (13.0 mmol) in argon. The reaction mixture was stirred for 12 h. On complete conversion of **1** by TLC, the resulting mixture was filtered through a short pad of Celite™ and concentrated under reduced pressure. A
15 flash column chromatography (hexane:ethyl acetate = 4:1) gave alkyne **12** (7.80 mmol). ¹H-NMR (400 MHz, CDCl₃): δ 0.91 (s, 18H), 2.25 (t, *J* = 2.4 Hz, 1H), 3.84 (dd, *J* = 6.4, 9.2 Hz, 2H), 4.30 (dd, *J* = 6.4, 8.4 Hz, 2H), 4.38 (dd, *J* = 8.4, 9.2 Hz, 2H), 4.69 (d, *J* = 2.4 Hz, 2H). ¹³C-NMR (100 MHz, CDCl₃): δ 24.5, 34.1, 39.9, 70.7, 71.5, 73.2, 79.4, 156.5.
20

Example 6: Preparation of the BOX Ligand 14a and 14b

The general procedure for click chemistry using **12** (0.80 mmol) and **3a** (0.75 mmol) gave **13a**. ¹H-NMR (400 MHz, CDCl₃): δ 0.60–0.65 (m, 2H), 0.85 (s, 18H), 1.97–2.00 (m, 2H), 3.57
25 (s, 9H), 3.79–3.83 (m, 2H), 4.24 (t, *J* = 6.4 Hz, 2H), 4.28–4.40 (m, 4H), 5.15 (bs, 2H), 7.63 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ 6.2, 24.0, 24.8, 25.5, 34.0, 50.6, 52.3, 70.2, 73.4, 122.9, 144.5, 157.0. MS (FAB): *m/z* (%) 511 (100) [M⁺+H], 453 (10), 268 (14). HRMS (FAB) calculated for
30 C₂₃H₄₃N₆O₅Si: 511.3059 [M⁺+H], found 511.3047.

The general procedure for click chemistry using **12** (0.80 mmol) and **3b** (0.75 mmol) gave **13b**. ¹H-NMR (400 MHz, CDCl₃): δ 0.79 (s, 18H), 3.63 (s, 9H), 3.77 (dd, *J* = 6.8, 9.2 Hz, 2H), 4.20 (dd, *J* = 6.8, 8.0 Hz, 2H), 4.30 (dd, *J* = 8.0, 9.2 Hz, 2H), 5.14 (s, 2H), 5.49 (bs, 2H), 7.27 (d, *J* = 8.4 Hz), 7.64 (d, *J* = 8.4 Hz). ¹³C-NMR (100 MHz, CDCl₃): δ 24.8, 25.5, 33.9, 50.9, 54.0, 70.2, 73.4, 122.9, 127.6, 130.2, 135.5, 137.0, 145.0, 157.0. MS (FAB): *m/z* (%) 559 (100) [M⁺+H], 306 (10), 268 (23). HRMS (FAB) calculated for C₂₇H₄₃N₆O₅Si: 559.3059 [M⁺+H], found 559.3051.

The general procedure for ligand grafting using **5** (2.50 g, 0.80 mmol TMS/g) and **13a** (0.75 mmol) gave **14a**. Elemental analysis, found: C, 9.36; H, 1.99; N, 2.00. Loading of ligand: 0.24 mmol/g.

The general procedure for ligand grafting using **5** (2.50 g, 0.80 mmol TMS /g) and **13b** (0.75 mmol) gave **14b**. Elemental analysis, found: C, 10.29; H, 1.94; N, 1.70. Loading of ligand: 0.21 mmol/g.

Procedure for Cyclopropanation

Cu(II) triflate (10 μmol) was added to **14a** (20 μmol) dispersed in THF. After stirring for 1 h, the suspension was filtered, washed with THF, and then dried under vacuum to give **15a**. Dodecane (0.5 mmol) and phenylhydrazine (25 μl of a 5 % solution) were added to a suspension of **15a** in DCM (3 ml). After addition of styrene (1.5 mmol), ethyl diazoacetate (1.0 mmol) in DCM (2 ml) was introduced dropwise over 5 h using a syringe pump. The mixture was stirred for an additional 2 h, and centrifuged. The solution portion was collected, and the trans/cis ratio and yield were determined by GC. The enantiomeric excess was

determined by GC using a ChiralDEX-B column. The precipitate was washed with DCM (5 ml) and centrifuged. The same rinsing procedure was repeated three times. The recovered catalyst was reused directly for the next run.

5 **Example 7: Organocatalysis**

Organocatalysts^[25] are attractive as they offer less expensive and environmentally benign processes. They may also be more readily amenable than metal-based catalysts to anchoring on a support for catalyst reuse.^[25] The

10 immobilisation of a metal-based catalyst on a support (generally achieved by anchoring an organic ligand followed by metal addition) is often plagued by metal leaching problems, and requires catalyst regeneration by metal replenishment before reuse.^[26]

15 Amino acids and their derivatives represent an obvious source of chiral organocatalysts.^[25] Their availability and different functionalities in the residues allow for a number of applications in the field of supported catalysis.^[27]

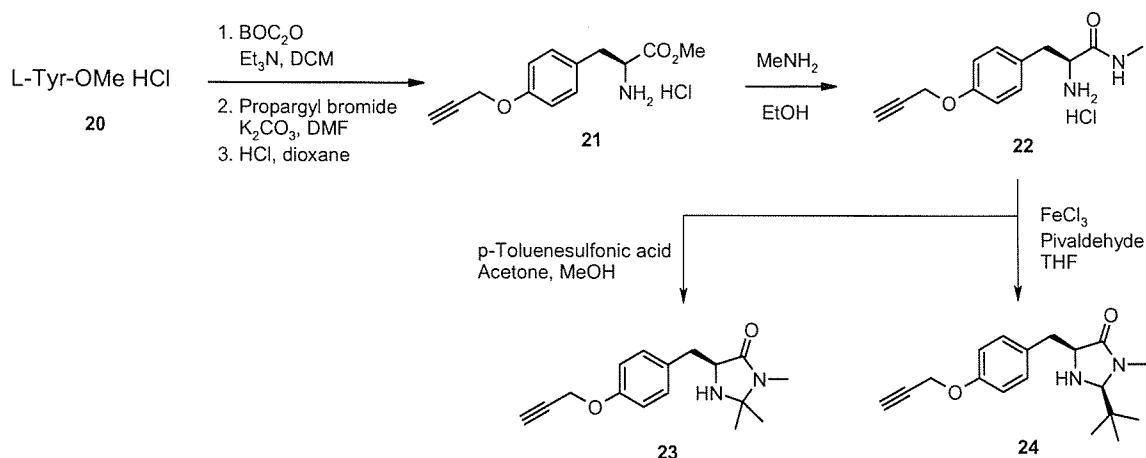
20 Recently, protonated phenylalanine-derived cyclic amines have emerged as versatile organic catalysts.^[28]

Imidazolidin-4-ones, originally proposed as organocatalysts by MacMillan and co-workers, have found widespread use in a number of processes.^[29] Their relevance led several groups to develop soluble and insoluble supported catalysts to
25 promote the enantioselective Diels-Alder cycloaddition, 1,3-dipolar cycloaddition, and Friedel-Crafts alkylation, etc.^[27,30]

The preparation of immobilized imidazolidin-4-ones is illustrated in Scheme 5.

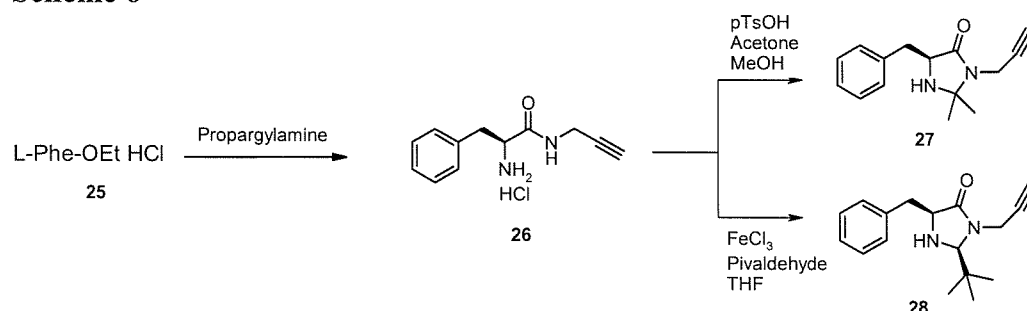
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Scheme 5



Starting from tyrosine methyl ester hydrochloride (**20**), of which free hydroxyl group would play a key part as a linkage to MCF, the alkynes **23** and **24** were synthesized in good yields by following the reported scheme (Scheme 5).^[28a, 31] Phenylalanine served as an alternative source of immobilized chiral imidazolidinones. A triple bond was successfully introduced by condensation of **25** and propargylamine in solvent-free conditions (Scheme 6).

Scheme 6



According to our previous synthetic methods, the alkynes **23/24/27/28** were further modified to append trimethoxysilane group by "clicking" with **3a/b** prior to the grafting onto MCF. These heterogenized organocatalysts **29–32** in Figure 1 proved to be useful for several reactions, providing good efficiency and selectivity as well as high recyclability.

Example 8: Preparation of Immobilised Organocatalysts 29–32

The general procedure for ligand grafting using **5** (2.00g, 0.60 mmol TMS/g) and a click chemistry product from the corresponding precursors **23** and **3a** (0.50 mmol, each) gave **29a**. Elemental analysis, found: C, 9.03; H, 1.89; N, 1.14.

5 Loading of catalyst: 0.16 mmol/g.

The general procedure for ligand grafting using **5** (2.00g, 0.60 mmol TMS /g) and a click chemistry product from the corresponding precursors **27** and **3a** (0.50 mmol, each) gave **31a**. Elemental analysis, found: C, 8.82; H, 1.91; N, 1.15.

10 Loading of catalyst: 0.16 mmol/g.

All publications, patents and patent applications cited in this specification are herein incorporated by reference as is each individual publication, patent or patent application
15 were specifically and individually indicated to be incorporated by reference. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of
20 prior invention.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily
25 apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

It must be noted that as used in this
30 specification and the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Unless defined otherwise

all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs.

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CLAIMS:

1. A method for preparing a heterogenised catalyst, comprising grafting a catalyst or catalyst precursor, via
5 click chemistry, to a siliceous mesocellular foam (MCF).
2. A method according to claim 1, wherein the grafting is effected at least in part by a 1,3-dipolar cycloaddition reaction.
3. A method according to claim 2, wherein the 1,3-
10 dipolar cycloaddition reaction is between an alkyne group and an azide group.
4. A method according to claim 2 or 3, wherein the 1,3-dipolar cycloaddition is carried out in the presence of a copper catalyst.
- 15 5. A method according to claim 4, wherein the copper catalyst comprises
 - (a) a source of copper(I), such as cuprous bromide or cuprous iodide, or
 - (b) a source of copper(II), such as copper(II)
20 sulfate, and a reducing agent, such as sodium ascorbate.
6. A method according to any one of claims 1 to 5, wherein the catalyst or catalyst precursor is grafted to the siliceous MCF through a 1,2,3-triazole.
7. A method according to any one of claims 1 to 6,
25 wherein the catalyst or catalyst precursor is grafted to the siliceous MCF by way of a linker moiety.
8. A method according to claim 7, wherein

the catalyst or catalyst precursor bears an alkyne group,

the linker moiety bears an azide group and a group that can react with the siliceous MCF, and

5 the grafting is carried out by reacting the catalyst or catalyst precursor to the linker moiety by way of a 1,3-dipolar cycloaddition reaction to form an intermediate, which intermediate is then reacted with the siliceous MCF.

10 9. A method according to claim 7, wherein

the catalyst or catalyst precursor bears an alkyne group,

the linker moiety bears an azide group and a group that can react with the siliceous MCF, and

15 the grafting is carried out by reacting the siliceous MCF to the linker moiety to form an intermediate, which intermediate is then reacted with the catalyst or catalyst precursor by way of a 1,3-dipolar cycloaddition reaction.

20 10. A method according to claim 8 or 9, wherein the group that can react with the siliceous MCF is a trialkoxy silyl group, such as a trimethoxy silyl group.

11. A method according to any one of claims 7 to 10, wherein the linker moiety has the formula:

25
$$\text{N}_3\text{-X-Si(OMe)}_3$$

wherein X is $\text{-CH}_2\text{CH}_2\text{-}$ or $\text{-C}_6\text{H}_4\text{-}$.

12. A method according to claim 7, wherein

the catalyst or catalyst precursor bears an azide group,

the linker moiety bears an alkyne group and a group that can react with the siliceous MCF, and

5 the grafting is carried out by reacting the catalyst or catalyst precursor to the linker moiety by way of a 1,3-dipolar cycloaddition reaction to form an intermediate, which intermediate is then reacted with the siliceous MCF.

10 13. A method according to claim 7, wherein

the catalyst or catalyst precursor bears an azide group,

the linker moiety bears an alkyne group and a group that can react with the siliceous MCF, and

15 the grafting is carried out by reacting the siliceous MCF to the linker moiety to form an intermediate, which intermediate is then reacted with the catalyst or catalyst precursor by way of a 1,3-dipolar cycloaddition reaction.

20 14. A method according to claim 12 or 13, wherein the group that can react with the siliceous MCF is a trialkoxy silyl group.

15. A method according to any one of claims 1 to 14, wherein the catalyst precursor is a ligand suitable to form
25 an organometallic ring-closing metathesis catalyst.

16. A method according to any one of claims 1 to 11, wherein the catalyst precursor is a derivative of a Hoveyda-Grubbs type ligand comprising an alkyne group or azide group.

17. A method according to any one of claims 1 to 14, wherein the catalyst precursor is a ligand suitable to form an organometallic cyclopropanation catalyst.

18. A method according to any one of claims 1 to 11, wherein the catalyst precursor is a derivative of a bisoxazoline comprising an alkyne group or azide group.

19. A method according to any one of claims 1 to 11, wherein the catalyst is an amino acid or amino acid derivative, comprising an alkyne group or an azide group.

20. A method according to any one of claims 1 to 11, wherein the catalyst is an imidazolidin-4-on derivative comprising an alkyne group or an azide group.

21. A method according to any one of claims 1 to 20, comprising a further step of converting the catalyst precursor to a catalyst.

22. A method according to claim 21, wherein the catalyst precursor is a ligand, and the converting step comprises reacting the catalyst precursor with a metal species and optionally further ligand molecules to form a heterogenised organometallic catalyst.

23. A heterogenised catalyst obtained by the method as defined in any one of claims 1 to 22.

24. A heterogenised catalyst comprising a catalyst species grafted onto a siliceous mesocellular foam (MCF) through a 1,2,3-triazole.

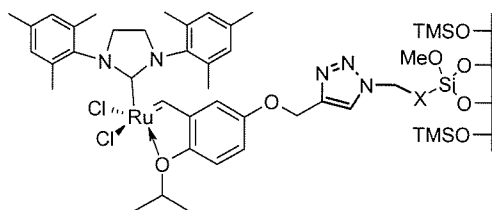
25. A heterogenised catalyst according to claim 24, wherein the catalyst species is grafted onto the siliceous MCF through a 1,4-adduct or a 1,5-adduct of the 1,2,3-triazole.

26. The heterogenised catalyst according to claim 24 or 25, wherein the catalyst is a ring-closing metathesis catalyst.

27. The heterogenised catalyst according to claim 26,
5 wherein the catalyst comprises ruthenium.

28. The heterogenised catalyst according to claim 26 or 27, wherein the catalyst comprises a Hoveyda-Grubbs type ligand.

29. The heterogenised catalyst according to claim 27,
10 which has a formula:



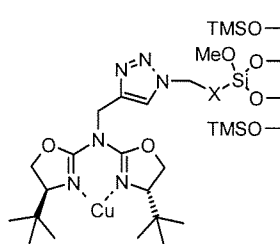
wherein X is $-\text{CH}_2\text{CH}_2-$ or $-\text{C}_6\text{H}_4-$.

30. The heterogenised catalyst according to claim 24 or 25, wherein the catalyst is a cyclopropanation catalyst.

15 31. The heterogenised catalyst according to claim 30, wherein the cyclopropanation catalyst is a bisoxazoline.

32. The heterogenised catalyst according to claim 30, wherein the cyclopropanation catalyst is an azabisoxazoline.

20 33. The heterogenised catalyst according to claim 30, wherein the cyclopropanation catalyst has the formula:



wherein X is $-\text{CH}_2\text{CH}_2-$ or $-\text{C}_6\text{H}_4-$.

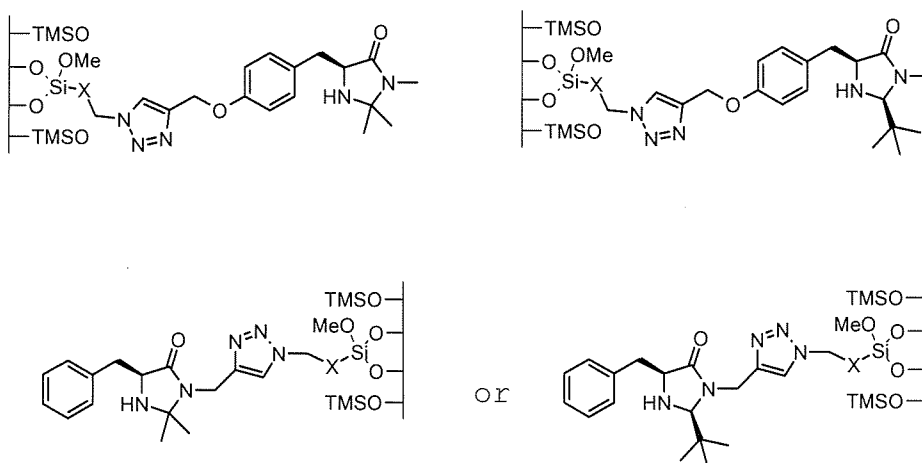
34. The heterogenised catalyst according to claim 24 or 25, wherein the catalyst is an organocatalyst.

5 35. The heterogenised catalyst according to claim 34, wherein the catalyst is an amino acid or an amino acid derivative.

36. The heterogenised catalyst according to claim 34, wherein the catalyst is a protonated phenylalanine-derived
10 cyclic amine.

37. The heterogenised catalyst according to claim 34, wherein the catalyst is an imidazolidin-4-one.

38. The heterogenised catalyst according to claim 34, which has the formula:



15

wherein X is $-\text{CH}_2\text{CH}_2-$ or $-\text{C}_6\text{H}_4-$.