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Synthesis and Catalytic Applications of C_3-Symmetric Tris(triazolyl)methanol Ligands and Derivatives

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Recently introduced tris(1,2,3-triazol-4-yl)methanols and derivatives (TTM ligands) have become a valuable subclass of C_3-symmetric tripodal ligands for transition metal-mediated reactions. TTM-based ligand architectures are modularly constructed through regioselective, one-pot triple [3+2] cycloaddition of azides and alkynes. Applications of homogeneous systems of this type and of heterogenized (polystyrene- and magnetic nanoparticle-supported) TTM ligands in synthesis and catalysis are compiled in this *Feature Article*.

1. Introduction and general remarks

The 1*H*-1,2,3-triazole scaffold is absent from natural structures; however, this heterocyclic unit finds ubiquitous presence in myriad synthetic compounds. In the early 60's of the last century, the discovery by Huisgen of the 1,3-dipolar thermal cycloaddition of azides and alkynes[1] triggered the first synthetic approaches towards triazole heterocycles. Nonetheless, it was not until the early 2000s, when the ground-breaking reports by the groups of Meldal,[2] and Fokin and Sharpless[3] on the copper-catalysed azide–alkyne cycloaddition (CuAAC) reactions for the highly efficient, regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles (Fig. 1) provided a definitive impulse to this area.[2,3] Extensive research on [3+2] cycloadditions of azides and alkynes prompted the discovery of the ruthenium-catalysed variant (RuAAC)[4] of the reaction, enabling synthetic access to 1,5-disubstituted 1,2,3-triazole regioisomers in a selective manner. Nowadays, the synthesis of 1,4-disubstituted 1,2,3-triazoles *via* CuAAC reactions[5] is considered as the paradigmatic example of click chemistry.[6] Thus, the process (Fig. 1) delivers in a predictable manner the target nitrogen-containing heterocycles (**C**) from their precursors (**A** and **B**) under mild conditions and with practically no limitations with respect to the functional groups on the reactants.

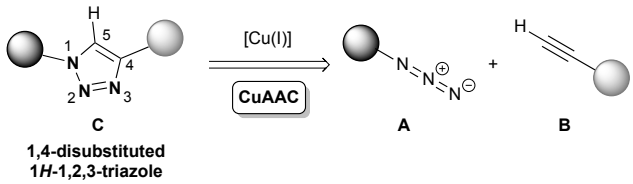


Fig. 1 Retrosynthetic approach to 1,4-disubstituted 1,2,3-triazoles *via* CuAAC.

Since its discovery, the CuAAC reaction has become a very commonly employed ligation tool. Given its reliability, specificity and biocompatibility, the CuAAC reaction has propelled the development of countless applications for triazole chemistry in diverse disciplines from pharmaceutical to materials science. Accordingly, 1,4-disubstituted 1,2,3-triazoles have emerged as valuable, yet readily available building blocks in the preparation of functional materials displaying an enormous wealth of unique properties.[7]

Regarding biomedical and biological applications, the profound impact of click reactions and triazole products in the vast field of medicinal chemistry has been extensively reviewed.[8] The triazole chemical inertness together with its inherent structural features converts this heterocycle into an excellent amide-bond surrogate (bioisosteric replacement). Consistently, triazole rings have been inserted into peptide sequences for the development of peptidomimetics that mimic the secondary structure of proteins, a topic of high relevance in chemical biology.[9] Another closely related important application of the CuAAC reaction arises from its bioorthogonality (*i.e.*, non-interacting with biological components while proceeding under physiological conditions, namely in aqueous medium under ambient temperature). This last feature has enabled the conjugation of several biomacromolecules –encompassing proteins, nucleic acids, lipids and glycans– with biophysical probes delivering biocompatible systems for both *in vitro* and *in vivo* studies.[10]

Concerning the preparation of triazole-based molecular architectures, CuAAC reactions have exerted a tremendous influence in the materials chemistry arena. Thus, the reaction has provided access to well-defined, complex polymeric materials (linear polymers, surfaces, star-shaped polymers),[11] functional polymers (stimuli-responsive hydrogels)[12] and also dendrimers.[13] Supramolecular chemistry has also benefitted from the diverse supramolecular interactions involving 1,2,3-triazoles.[14] In this context, click-derived triazoles have led to a wide range of supramolecular functional systems,[14,15] applications as chemical sensors or receptors for the molecular recognition of metal ions being noteworthy.[16]

Threefold rotational symmetry, structural modularity and other key aspects of ligand design have played a crucial role in the development of new types of chelating tripodal ligands.[17] Due to the beneficial influence of molecular symmetry in catalytic reactions, the design and preparation of C_3-symmetric ligands and of their metal complexes has found numerous successful applications in homogeneous catalysis.[18] C_3-Symmetric tripodal ligands typically coordinate to metal atoms in a tridentate fashion. This topology of ligation is found, for instance, in tris(pyrazolyl)borates[19] (**I**, Fig. 2), the most common example of scorpionate multidentate ligands.[20] Monoanionic tris(pyrazolyl)borates are amongst the most versatile tridentate ligands for transition-metal coordination and their complexes have been extensively applied in diverse catalytic transformations.[19] The analogous tris(pyrazolyl)alkanes[21] (**II**, Fig. 2), bearing a carbon atom as the central bridging apex, have received much less attention likely because of their limited synthetic accessibility. Tris(2-pyridyl)methanes[22] (**III**, Fig. 2) and tris(oxazolinyl)ethanes[23] (**IV**, Fig. 2) represent other related ligand platforms of the same class. Chiral tris(oxazolinyl) ligands, in particular, have been successfully applied in asymmetric catalysis.[23]

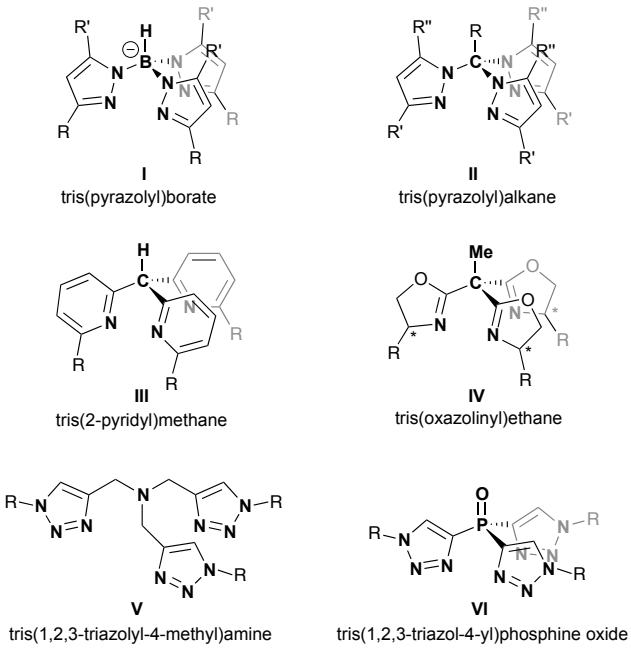


Fig. 2 Representative structures of selected C_3-symmetric tripodal ligand architectures.

Given the broad applicability of the CuAAC reaction,[5] it is not surprising that different C_3-symmetric tripodal ligands containing three equivalent 1,2,3-triazole rings and constructed through this methodology have been reported. Tris(1,2,3-triazolyl-4-methyl)amines (**V**, Fig. 2), and more precisely tris(benzyltriazolylmethyl)amine (TBTA)[24] and its derivatives[25] have shown to be versatile ligands for transition metal complexation. In particular, the derived copper(I) complexes[26] depict impressive rate-accelerating ligand effects in a wide range of CuAAC reactions.[5,24,25]

Click-derived phospha-scorpionates constitute a much less studied family of symmetrical tripodal ligand architectures.[27] In spite of the rich coordination chemistry of the air stable tris(1,2,3-triazolyl)phosphine oxide[27a,c,d,f] scorpionates (**VI**, Fig. 2) and of the air-sensitive tris(1,2,3-triazolyl)phosphine[27a,b,e] ligands, no examples of catalytic applications of these species have been reported in the literature.

Starting from the consideration of the coordination possibilities offered by 1,2,3-triazoles,[28] and bearing in mind the convenience of a simple and versatile approach to tripodal ligands based on this structure, we realised some years ago the potential offered by the tris(triazolyl)methanol (TTM) structure (**VII**) in coordination and catalysis.[29] As shown in Fig. 3, the TTM ligands should be readily accessible from simple precursors through a modular approach that also creates the tertiary alcohol as an innate feature. Modulation of the TTM ligands should be possible by simple modification of R groups derived from azido precursors, while the alcohol moiety should allow derivatisation and immobilisation onto solid supports.

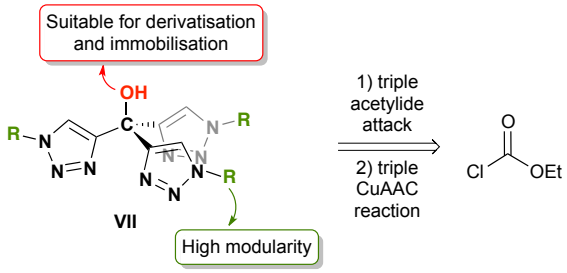
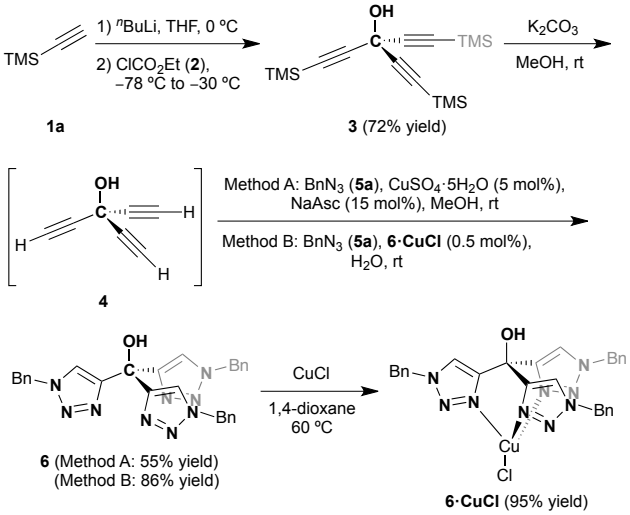


Fig. 3 Retrosynthetic analysis of the generic TTM-based ligand structure.

The present *Feature Article* is intended to provide an overview of the chemistry and catalytic applications of TTM ligands and derivatives. The discussion has been organised to discuss first the synthetic approaches leading to the preparation of TTM ligand derivatives. The role of TTM ligands in homogeneous catalysis is next discussed, followed by a summary of the synthetic applications of the CuCl complex of the originally developed TTM ligand and by a final section dealing with recently reported applications of immobilised (polystyrene- and magnetic nanoparticle-supported) TTM ligands in heterogeneous catalysis.

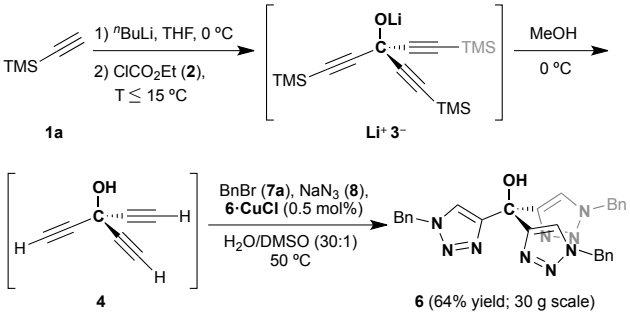
2. Preparation of TTM ligand derivatives

Tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol (**6**), the originally developed TTM ligand, was reported in 2009.[29] The original preparation of **6** (Scheme 1) started with the one-pot synthesis of tris[(trimethylsilyl)ethynyl]methanol (**3**) in 72% yield from trimethylsilylacetylene (**1a**) and ethyl chloroformate (**2**). The protodesilylation of **3** with methanol under basic conditions led to tris(ethynyl)methanol (**4**), which was not isolated. Subsequent triple CuAAC reaction of tris(alkyne) **4** with benzyl azide (**5a**) under classical conditions (method A, Scheme 1) furnished the target TTM ligand **6** in 55% overall yield (from **2**). Treatment of **6** with a stoichiometric amount of CuCl in 1,4-dioxane at 60 ºC rendered the neutral copper(I) complex **6·CuCl**[30] in almost quantitative yield (Scheme 1). Interestingly, **6·CuCl** turned out to be stable in open air, and this fact was attributed to efficient chelation by the TTM ligand. Complex **6·CuCl** was also used in the absence of any additive or base to catalyse the triple CuAAC reaction of **4** with **5a** in water[31] at rt (method B, Scheme 1). Gratifyingly, a very reduced catalyst loading of **6·CuCl** (0.5 mol%) was sufficient to promote the triple cycloaddition, affording the TTM ligand **6** in a highly improved 86% overall yield.



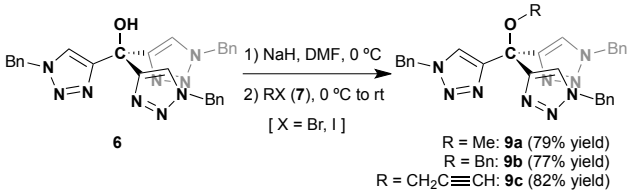
Scheme 1 Original preparation of the TTM ligand **6** and **6·CuCl**.

An alternative approach to tris(triazolyl)methanol **6** was later reported by Génisson and Chauvin and co-workers,[32] involving a three-step sequence for the preparation of **3** and a triple tandem desilylation–CuAAC process.[33]
Pericàs and co-workers[34] recently developed a safe and practical, one-stage procedure for the large-scale (50–100 mmol) preparation of **6** (Scheme 2). The optimised one-pot protocol avoided the use of potentially hazardous reagents and solvents, did not require any chromatographic purification and proceeded without the isolation of any reaction intermediate. As a salient feature, the triple CuAAC reactions were conducted in three-component mode,[35] avoiding the use of benzyl azide.[36]



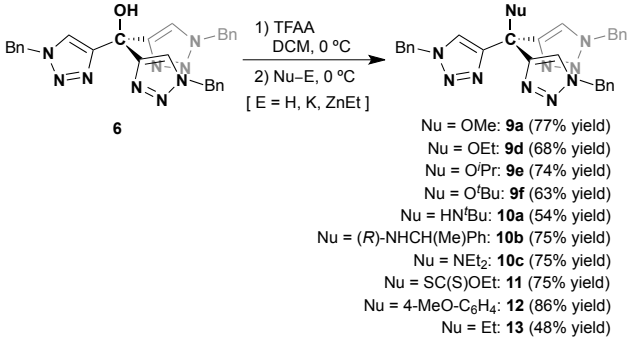
Scheme 2 Optimised one-pot procedure for large-scale preparation of TTM ligand **6**.

As already mentioned, the free hydroxyl group present in **6** offers opportunity for further derivatisation of TTM ligands. Taking advantage of this structural feature, the TTM ligand **6** was transformed in high yields (77–82%) into the tris(triazolyl)methyl ethers **9a–c** by Williamson-type etherification reactions (Scheme 3).[34,37]

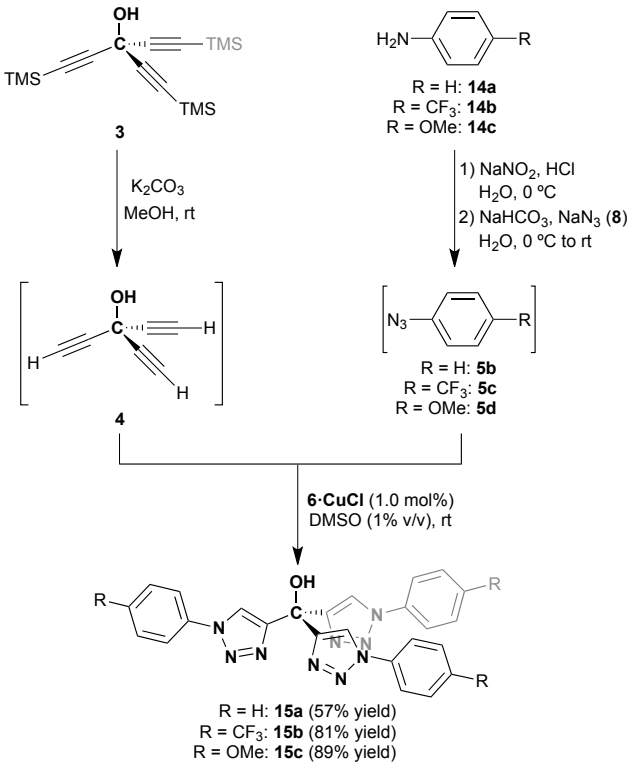


Scheme 3 Derivatisation of TTM ligand **6** into tris(triazolyl)methyl ethers **9a–c**.

A versatile approach to tris(triazolyl)methyl derivatives **9–13** was alternatively reported[32] by exploiting the generation and trapping of the tris(1-benzyl-1,2,3-triazol-4-yl)carbenium cation, a heterocyclic analogue of the well-studied trityl cation. Thus, treatment of **6** with trifluoroacetic anhydride (TFAA) led to the intermediate carbocation, which could be trapped with a wide array of oxygen, nitrogen, sulfur and carbon nucleophiles (Scheme 4).



Scheme 4 Preparation of TTM derivatives **9–13** by trapping of the tris(1-benzyl-1,2,3-triazol-4-yl)carbenium cation.



Scheme 5 Syntheses of tris(aryltriazolyl)methanol ligands **15a–c**.

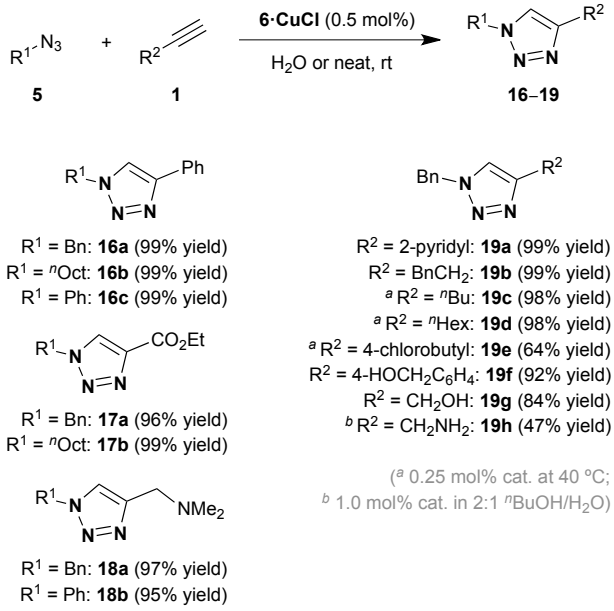
The high structural modularity of the C_3-symmetric TTM ligands also facilitates the introduction of different sets of substituents at the

N1 atoms in the three equivalent triazole rings. Aryl groups, for instance, can be introduced by simply using aryl azides as reactive partners in the triple CuAAC reaction of the key intermediate **4**. Pericàs and co-workers[34] prepared in this way the tris(1-aryl-1*H*-1,2,3-triazol-4-yl)methanol ligands **15a–c** bearing neutral (**15a**), electron-withdrawing (**15b**) or electron-donating (**15c**) *para*-substituents with the purpose of modulating the catalytic behaviour of their metal complexes through fine-tuning of electronic properties (Scheme 5). Parallel linear sequences were telescoped simultaneously towards the synthesis of tris(aryltriazolyl)methanols **15a–c**, which could be isolated in fair to excellent yields (57–89%) after a single recrystallization.

3. Applications of TTM ligands in homogeneous catalysis

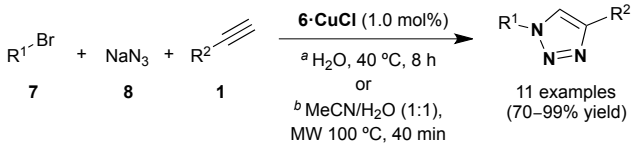
The accelerating effect of the TTM ligand **6** in CuAAC reactions performed in aqueous media[31] has already been shown above (see Schemes 1, 2 and 5). The presence of the free OH group in the ligand template confers some hydrophilic character to **6·CuCl**, while the tight chelate structure efficiently protects the metal centre against undesired oxidation or disproportionation leading to inactive Cu(II) species. Probably for these reasons, such a well-defined copper(I) complex[38] is finding increasing application within the vast territory of click chemistry.

The catalytic performance of **6·CuCl** was initially scrutinised by conducting a variety of CuAAC reactions in water or under neat conditions[29] (Scheme 6). By using a very low catalyst loading (0.5 mol%) under ambient conditions (inert atmosphere not required) a palette of 15 different 1,4-disubstituted-1,2,3-triazoles (**16–19**) was readily obtained. Notably, **6·CuCl** exhibited high functional group tolerance as substrates containing functional groups (primary amines) with high binding ability for copper gave rise to the corresponding triazole products (**19h**).



Scheme 6 Catalytic performance of **6·CuCl** in cycloaddition reactions of azides (**5**) and terminal alkynes (**1**) on water or under neat conditions.

The three-component tandem version of the CuAAC reaction[35] catalysed by complex **6·CuCl** (1.0 mol%) was also explored.[29] By following this safe and convenient synthetic approach, a total of 11 triazoles were efficiently prepared in good to excellent yields (Scheme 7) *via in situ* formation of *n*-octyl or benzyl azides from the corresponding bromides (**7**) and sodium azide (**8**). Two different click methods were used involving either smooth heating in water[31] at 40 ºC or microwave (MW) activation[39] at 100 ºC in MeCN/H_2O (1:1), the latter protocol involving much shorter reaction times.

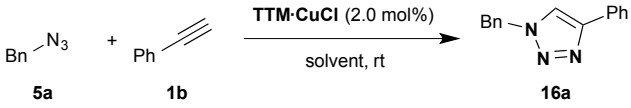


Scheme 7 Three-component azide-alkyne cycloaddition reactions catalysed by **6·CuCl**.

Tris(triazolyl)methyl ethers **9a** and **9b** (see Scheme 3) and tris(aryltriazolyl)methanols **15a–c** (see Scheme 5) have also been used as accelerating ligands for CuAAC reactions.[34] A comparative study of the catalytic efficiency exhibited by neutral copper(I) complexes of TTM derivatives in different solvents (water, *n*-hexane, toluene, DCM, THF, MeCN) was performed using the cycloaddition between benzyl azide (**5a**) and phenylacetylene (**1b**) as the model reaction. The catalyst loading of **TTM·CuCl** was fixed at 2.0 mol% in all the

organic media whereas it was reduced down to 0.5 mol% in water. A detailed analysis of the whole set of results (Table 1; conversions higher than 90% marked in bold) confirmed the excellent catalytic performance of **6·CuCl** in water. Very remarkably, phenyl- (**15a**) and *p*-trifluoromethyl-substituted (**15b**) ligands behaved notoriously well in almost every tested reaction solvent. Taking into account the solubility characteristics of 1,2,3-triazoles, the Cu(I) complexes of **15a** and **15b** could be of particular importance for cascade sequences requiring triazole products to be kept in solution.

Table 1 Comparative outcome and solvent effect in the model cycloaddition reaction of benzyl azide (**5a**) with phenylacetylene (**1b**) catalysed by **TTM·CuCl** complexes.

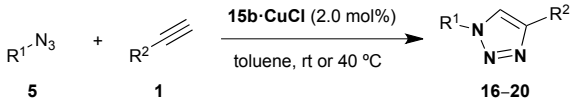


5a **1b** **16a**

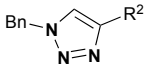
TTM[a]	water[b] (4 h)	*n*-hexane (6 h)	toluene (6 h)	DCM (6 h)	THF (16 h)	MeCN (16 h)
6	**98**	5	75	25	90	21
9a	56	27	69	**99**	60	89
9b	**99**	43	26	**98**	**92**	**96**
15a	**99**	**99**	**98**	**95**	78	86
15b	82	**99**	**99**	**99**	80	50
15c	**99**	14	2	22	3	10

[a] Results given as % conversion. [b] 0.5 mol% catalyst loading.

Given the excellent catalytic performance of **15b·CuCl** for CuAAC reactions in toluene, the use of this catalyst/solvent combination was further investigated.[34] By using the reaction conditions shown in Scheme 8, a total of 17 different 1,4-disubstituted-1,2,3-triazoles (**16**–**20**) were readily prepared in good to excellent yields (74–99%). Not only benchmark organic azides (**5**) and terminal alkynes (**1**) but also other more challenging substrates bearing functional groups such as esters, amines, alcohols or carbamates were all compatible with this methodology. The synthetic usefulness of **15b·CuCl** was demonstrated with the successful preparation of triazole-linked, chiral organocatalysts precursors such as pyrrolidine derivative **17d**[40] and proline derivatives **16e** and **17e**[41] (Scheme 8). Another remarkable application of **15b·CuCl** in toluene enabled the synthesis of C_3-symmetric tris(triazole)-containing structures **20a** and **20b** (Scheme 8). Functionalised compounds **20a** and **20b** constitute valuable building blocks for the assembly of supramolecular polymers based on hexasubstituted benzene scaffolds.[42]

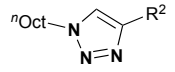


5 **1** **16**–**20**

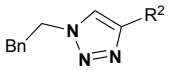


R^2 = Ph: **16a** (99% yield)
R^2 = CO_2Et: **17a** (85% yield)
[a,b] R^2 = CH_2NMe_2: **18a** (99% yield)
R^2 = 4-$HOCH_2C_6H_4$: **19f** (80% yield)
[a] R^2 = $C(Me)_2OH$: **19i** (95% yield)
R^2 = CH(Ph)OH: **19j** (95% yield)
R^2 = 4-$H_2NC_6H_4$: **19k** (74% yield)
[a] R^2 = CH_2O_2CMe: **19l** (99% yield)

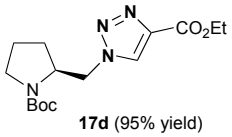
([a] In 1:1 ^{t}BuOH/H_2O; [b] 1.0 mol% cat.)



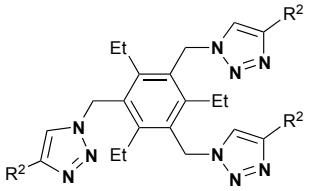
R^2 = Ph: **16b** (99% yield)
R^2 = CO_2Et: **17b** (99% yield)



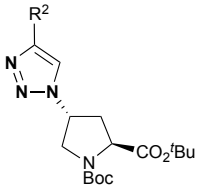
R^2 = Ph: **16d** (99% yield)
R^2 = CO_2Et: **17c** (93% yield)



17d (95% yield)



R^2 = CO_2Et: **20a** (99% yield)
R^2 = $C(Me)_2OH$: **20b** (80% yield)



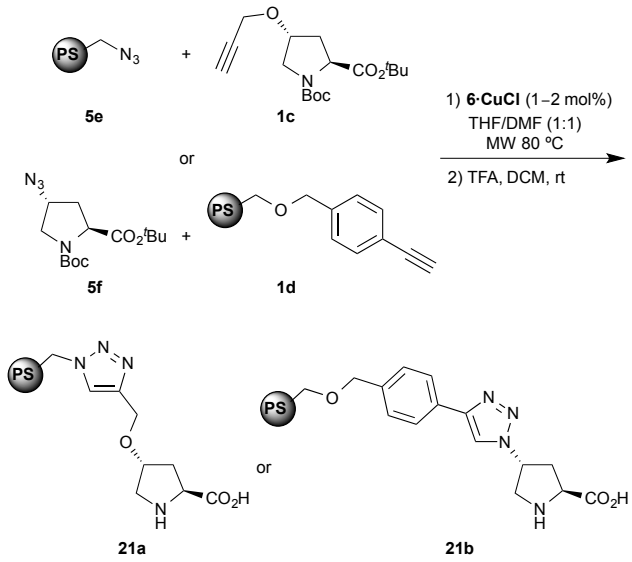
R^2 = Ph: **16e** (99% yield)
R^2 = CO_2Et: **17e** (99% yield)

Scheme 8 Substrate scope of the best performing TTM-based catalytic system for CuAAC in toluene (**15b·CuCl**).

The suitability of **15b·CuCl** as the catalyst in three-component CuAAC reactions,[35] involving *in situ* formation of organic azides from suitable bromide precursors and sodium azide, could also be demonstrated.[34] These tandem, one-pot processes were conducted in a MeCN/H_2O (1:1) solvent mixture under MW-accelerated conditions[39] and afforded triazole products in moderate to excellent yields.
Besides the applications of TTM ligands in CuAAC reactions, it is worth mentioning a very recently reported contribution by Taran *et al.*[43] where the TTM ligand **6** was applied in the Cu-catalysed sydnone–alkyne cycloaddition (CuSAC).[44]

4. Synthetic applications of 6·CuCl

The use of CuAAC reactions for the covalent immobilisation of chiral ligands and catalysts onto solid supports has found widespread applications in asymmetric catalysis.[45,46] In addition to the wide applicability of this immobilisation strategy, the resulting triazole tether is thermally stable under standard reactions conditions and chemically inert towards most solvents and reactants, thus minimising potential leaching issues.[45] Another advantage of this strategy relies on the large dipole moment of the 1,2,3-triazolyl moiety that plays a pivotal role in the overall hydrophilic character of the catalyst system and confers an enhanced compatibility with polar solvents.[46b]
Pericàs and co-workers, who reported for the first time a click-based approach for the immobilisation of a chiral organocatalytic system,[47] have further developed this field by introducing a variety of immobilised, triazole-linked chiral organocatalysts as highly recyclable and enantioselective mediators. In these studies, formation of the triazole unit through CuAAC reaction has been mostly accomplished by using **6·CuCl** as the catalyst for its high functional group tolerance and high activity at low loadings under mild reaction conditions.

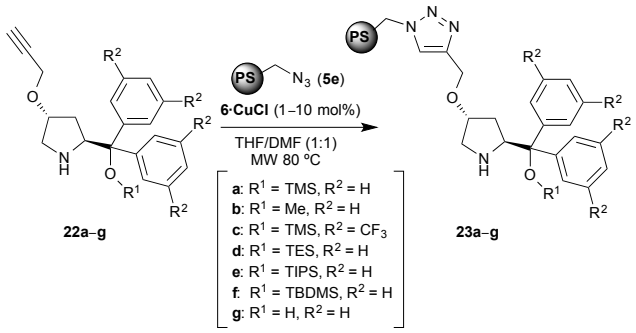


Scheme 9 Synthesis of PS-supported triazole-linked chiral proline derivatives **23a** and **23b** by using **6·CuCl**.

Proline derivative **21a** has been prepared from 4-propargyloxyproline derivative **1c** and azidomethylpolystyrene **5e** through MW-promoted CuAAC reaction catalysed by **6·CuCl** followed by deprotection (Scheme 9).[48] The PS-supported derivative **21a** has been used in the highly enantioselective α-aminoxylation of aliphatic aldehydes under continuous flow conditions.[48] The same organocatalytic system was previously applied to the asymmetric α-aminoxylation of aldehydes and ketones under bath conditions,[49] for the direct enantioselective aldol reactions in batch[41,47] and for highly enantioselective, *syn*-diastereoselective Mannich reactions in batch and flow.[50] Another immobilised chiral proline derivative (**21b**), which contains a longer spacer between the triazole ring and the polymer backbone, was designed for higher catalytic activity and allowed the development of the first practical flow version of highly enantioselective aldol reactions.[51] The PS-supported organocatalyst **21b** was efficiently prepared by click reaction between 4-azidoproline derivative **5f** and PS-functionalised alkyne **1d** catalysed by **6·CuCl** under MW irradiation, and subsequent acidic cleavage of protecting groups (Scheme 9). The applicability of **21b** in packed-bed reactors for the sequential preparation in flow of a series of aldol adducts with very high diastereo- and enantioselectivities was shown.[51]
A series of PS-supported triazole-linked chiral diarylprolinol derivatives **23a–g** was efficiently prepared by click reaction between azidomethylpolystyrene **5e** and 4-propargyloxydiarylprolinol derivatives **22a–g** by using **6·CuCl** under MW irradiation (Scheme 10). Compound **23a** proved to be a recyclable organocatalyst with enzyme-like selectivity in the asymmetric Michael additions of linear aldehydes to β-nitrostyrenes.[52] Different Michael additions were explored in depth by using the trimethylsilyl ether **23a** as well as the methyl ether **23b**, with the best performing organocatalytic system **23a** being also applied in enantioselective Michael-type additions of malonates or nitromethane to α,β-unsaturated aldehydes.[53] The catalytic performance of phenyl- and 3,5-bis(trifluoromethyl)phenyl-substituted diarylprolinol derivatives **23a** and **23c**, respectively, was compared in the enantioselective Michael–Knoevenagel domino

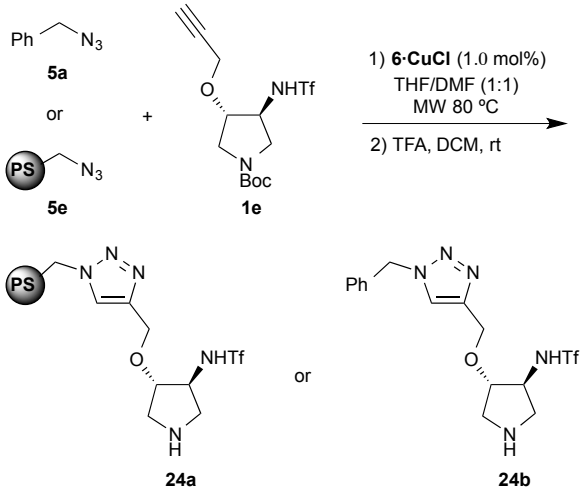
reaction of dimethyl 3-oxoglutarate and α,β-unsaturated aldehydes.[54] Immobilised diphenylprolinol silyl ethers **23d–f** (Scheme 10) were developed to prevent deactivation by silyl ether hydrolysis as previously observed with **23a**[52,53] and were successfully applied in the asymmetric α-amination of linear aldehydes with dibenzyl azodicarboxylate.[55] The optimal system **23f** showed very good recyclability under batch conditions and allowed long-standing continuous flow operation.

On the other hand, PS-supported chiral diphenylprolinol derivative **23g** (Scheme 10) was tested as a chiral organocatalyst in the enantioselective cross-aldol reaction of acetaldehyde and 4-nitrobenzaldehyde mediated by a dual catalytic system operating under site isolation conditions.[56]



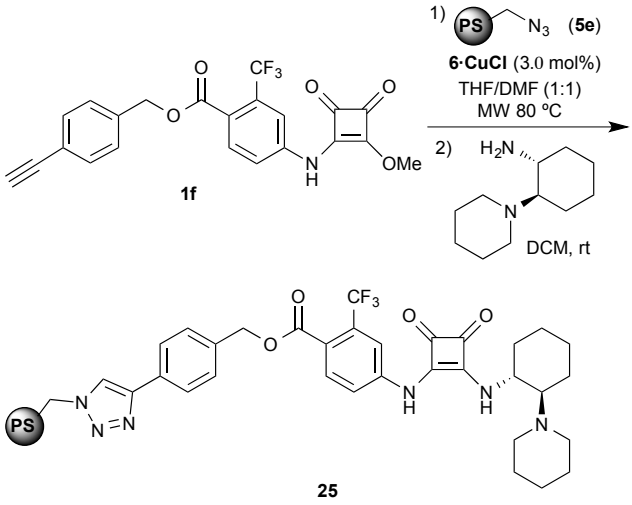
Scheme 10 Synthesis of PS-supported triazole-linked chiral diarylprolinol derivatives **23a–g** by using **6·CuCl**.

Catalyst **6·CuCl** was also used for the preparation of PS-supported (**24a**) and monomeric (**24b**) triazole-linked chiral 3-aminopyrrolidine derivatives by MW-accelerated click reaction between 4-propargyloxypyrrolidine derivative **1e** and azidomethylpolystyrene (**5e**) or benzyl azide (**5a**), respectively, followed by TFA-mediated *N*-Boc deprotection (Scheme 11). Pyrrolidine derivatives **24a** and **24b** were introduced as extremely active organocatalysts for asymmetric *anti*-selective Mannich reactions, and the supported one (**24a**) allowed the implementation of a robust continuous flow process suitable for the sequential preparation of small libraries of *anti*-selective Mannich products and for the large-scale production of single Mannich adducts.[57]



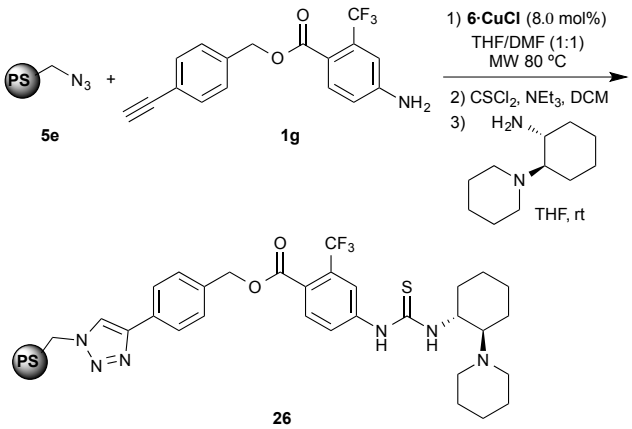
Scheme 11 Synthesis of PS-supported (**24a**) and monomeric (**24b**) triazole-linked chiral 3-aminopyrrolidine derivatives by using **6·CuCl**.

Catalyst **6·CuCl** also allowed the immobilisation of squaramide organocatalysts onto polystyrene. Thus, the PS-supported chiral squaramide **25** was accessible in two steps through an initial MW-promoted CuAAC reaction between the alkyne-functionalised precursor **1f** and azidomethylpolystyrene **5e**, followed by reaction with a suitable enantiopure *trans*-1,2-diaminocyclohexane derivative (Scheme 12). The resulting squaramide **25** was used as a highly recyclable organocatalyst for enantioselective Michael additions of 1,3-dicarbonyl compounds to β-nitrostyrenes in batch[58] and flow.[59]



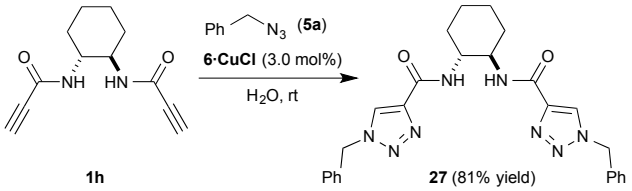
Scheme 12 Synthesis of PS-supported triazole-linked chiral squaramide **25** by using **6·CuCl**.

Following a closely related synthetic strategy, the PS-supported chiral thiourea **26** was prepared through a three-step sequence involving **6·CuCl**-catalysed CuAAC reaction of **5e** with terminal alkyne **1g**, isothiocyanate formation and final integration of an enantiopure *trans*-1,2-diaminocyclohexane derivative (Scheme 13). Thiourea **26** has shown very high activity and enantioselectivity in the α-amination of cyclic 1,3-dicarbonyl compounds with azodicarboxylates under batch and continuous flow modes.[60]



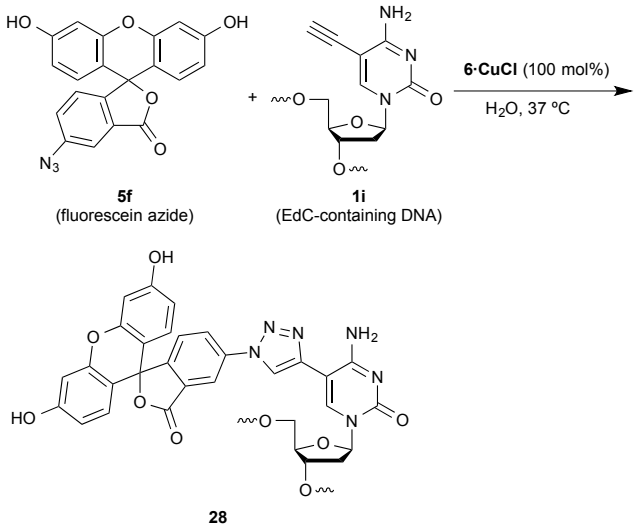
Scheme 13 Synthesis of PS-supported triazole-linked chiral thiourea derivative **26** by using **6·CuCl**.

Apart from the development of triazole-linked chiral organocatalytic systems, catalyst **6·CuCl** has also been successfully applied to the preparation of triazole-containing ligands for homogeneous metal catalysis. The click reaction between benzyl azide (**5a**) and bis(alkyne) **1h** catalysed by **6·CuCl** afforded the C_2-symmetric bis(triazolecarboxamido) derivative **27** in 81% yield (Scheme 14). Compound **27** was used as a tetradentate chiral ligand for molybdenum-catalysed asymmetric allylic alkylation reactions, with very high regio- and enantioselectivities being recorded under thermal or MW-promoted conditions.[61]



Scheme 14 Synthesis of C_2-symmetric bis(triazolecarboxamido) ligand **27**.

Catalyst **6·CuCl** has also found use in the preparation of materials for non-catalytic purposes. An interesting application in the area of biochemistry was developed by Bortvin and Greenberg *et al.*[62] The click reaction between fluorescein azide (**5f**) and alkyne-functionalised 5-ethynyl-2'-deoxycytidine (EdC)-containing DNA **1i** mediated by **6·CuCl** under physiological conditions enabled the fluorescence labelling of DNA fragments[63] (Scheme 15). The so obtained fluorophore-conjugated DNA **28** constitutes a valuable visualisation tool for exploring the chemical mechanism of DNA demethylation.



Scheme 15 Fluorescence labelling of EdC-containing DNA (**1i**) *via* CuAAC by using **6·CuCl**.

Pericàs, Ros and co-workers envisioned applications of **6·CuCl** for the preparation of liquid crystalline materials.[64] These authors prepared a library of symmetrical and non-symmetrical oligomers (**29**) by CuAAC reaction between suitable azide- and alkyne-ended building blocks catalysed by **6·CuCl**. Compounds **29** (Fig. 4) are bent-shaped structures featuring 1,2,3-triazole rings as the central core. Such bent-core assemblies exhibited liquid crystalline properties ranging from lamellar to columnar or B4-like supramolecular organisations.

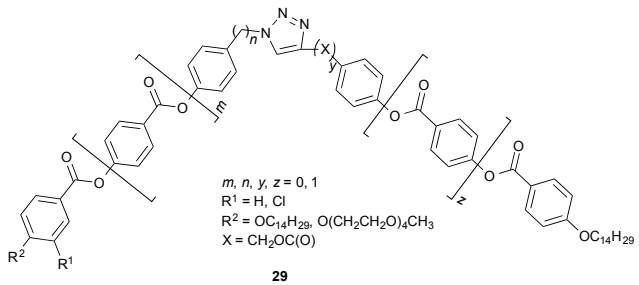


Fig. 4 Bent-core triazole-based liquid crystalline materials (**29**) prepared by CuAAC using **6·CuCl** as the catalyst**.**

The group of Lyle Isaacs has extensively used catalyst **6·CuCl** as a tool for the preparation of triazole-functionalised cucurbituril[65] (CB) derivatives (**30–32**; Fig. 5), readily accessible through building block-based click approaches. Cucurbit[n]uril (n = 5–10) chemistry delivers exceptional recognition properties of these pumpkin-shaped supramolecular macrocycles towards organic and inorganic guests.[66] Cucurbit[6]uril derivative **30** features a CB[6] sized cavity covalently bound to an isobutylammonium tail through a 1,2,3-triazole linker. Self-assembly of CB[6] **30** in water as a cyclic [c2] daisy chain showed responses to chemical stimuli in the form of competing guests and hosts.[67] Similarly, CB[7] derivative **31a**, which bears a triazole-linked primary alkyl ammonium chloride group, underwent a self-assembly process into a cyclic tetramer and showed outstanding host-guest recognition properties.[68] Closely related hydrophobic CB[7] derivatives **31b** and **31c**, bearing triazole-linked secondary alkyl ammonium bromide residues, formed self-inclusion complexes leading to vesicle-type supramolecular assemblies by addition of guests.[69] Finally, two monofunctionalised propargyloxy-CB[6] and CB[7]-azide derivatives were converted into CB[6]-CB[7] heterodimer **32** by click chemistry using **6·CuCl** as the catalyst. Self-sorting assembly of heterodimer **32** delivered hydrophobic or amphiphilic block copolymers giving rise to supramolecular networks and micelles.[70]

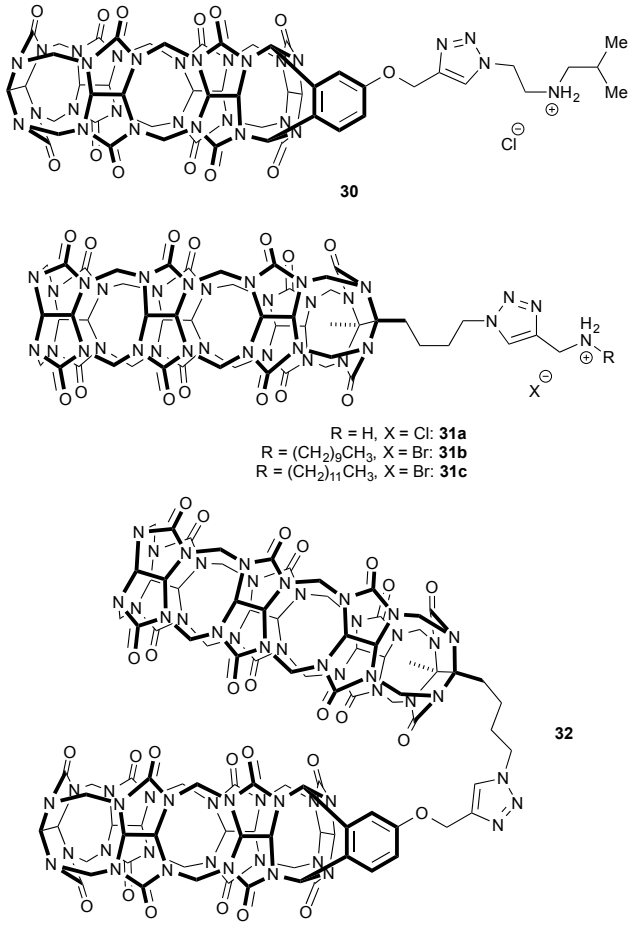
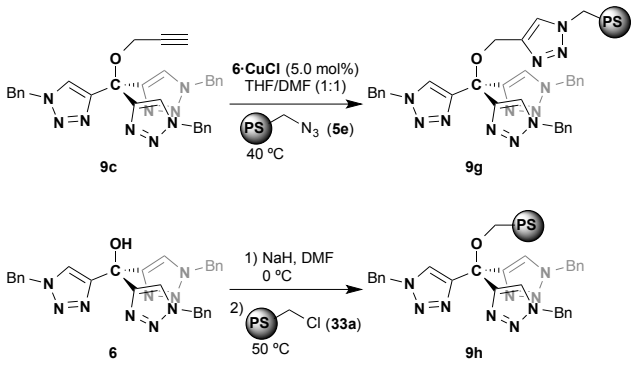


Fig. 5 Triazole-functionalised supramolecular structures of CB[6] (**30**) and CB[7] (**31a–c**) derivatives as well as CB[6]–CB[7] heterodimer (**32**) prepared by CuAAC using **6·CuCl.**

5. Immobilised TTM ligands in heterogeneous catalysis

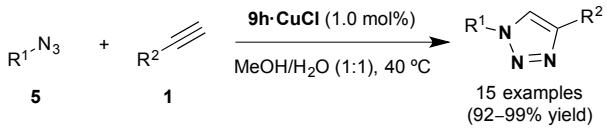
Immobilisation of catalysts and ligands onto solid supports can lead to important sustainability improvement whenever the activity of the homogeneous system is retained and the supported system admits multiple recycling.[45,46] As an additional bonus, heterogenised systems can be separated by simple filtration, with suppression of wasteful work-up treatments.

In this context, Pericàs and co-workers[37] reported on the grafting of monomeric tris(triazolyl)methanol **6** and tris(triazolyl)methyl propargyl ether **9c** onto polystyrene derivatives through two complementary strategies (Scheme 16). In both cases the innate OH group present in the TTM ligands is used as the immobilisation point. This leaves the tris(triazolyl)methyl scaffold unperturbed by the polymer backbone, thus favouring the preservation of catalytic activity. A click-based approach was initially followed to support the propargyl ether **9c** onto azidomethylpolystyrene **5e**. Alternatively, etherification of the free hydroxy group in **6** with Merrifield resin **33a** was performed *via* S_N2 reaction. These strategies yielded PS-supported tris(triazolyl)methyl ethers **9g** and **9h** featuring triazole and ether linkages, respectively. Neutral copper(I) complexes of **9g** and **9h** were formed by treatment of the immobilised ligands with a stoichiometric amount of CuCl in THF, and the resulting complexes (**9g·CuCl** and **9h·CuCl**) were successfully used as catalysts in CuAAC reactions.[37]



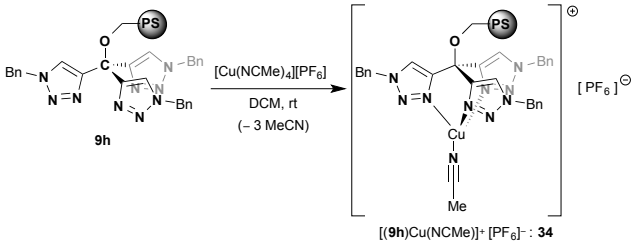
Scheme 16 Immobilisation strategies leading to PS-supported tris(triazolyl)methyl ether ligands **9g** and **9h**.

When testing a model CuAAC reaction, the simple, ether-linked supported system **9h·CuCl** exhibited superior catalytic performance and recyclability in comparison to the triazole-linked system **9g·CuCl**.[37] Indeed, complex **9h·CuCl** proved to be very active at low catalyst loading (1.0 mol%) and low concentration (down to 0.125 M) in both aqueous and organic media. The best results were obtained in a MeOH/H_2O (1:1) solvent mixture, which enabled efficient recycling and reuse of the catalytic system for five consecutive cycles. Additionally, the useful life of resin **9h** could be unlimitedly extended by simply reloading it with CuCl every five reaction cycles.
The applicability of the heterogenized system **9h·CuCl** for the CuAAC reaction between different azides and various alkynes under optimised reaction conditions (Scheme 17) was subsequently studied. A representative set of 15 different 1,4-disubstituted 1,2,3-triazoles featuring many different functionalities (alcohols, amines, esters, carboxylic acids, nitro groups, silyl ethers) was prepared in very high yields (92–99% yield) and short reaction times at low catalyst loading (1.0 mol%). In all cases the product isolation was readily accomplished by simple filtration (with full recovery of **9h·CuCl**). The low catalyst loading and high recyclability of **9h·CuCl** boded a very reduced leaching of copper into the aqueous/alcohol reaction media, as confirmed by UV-Vis spectroscopy analyses of several batches of triazole **16a**.

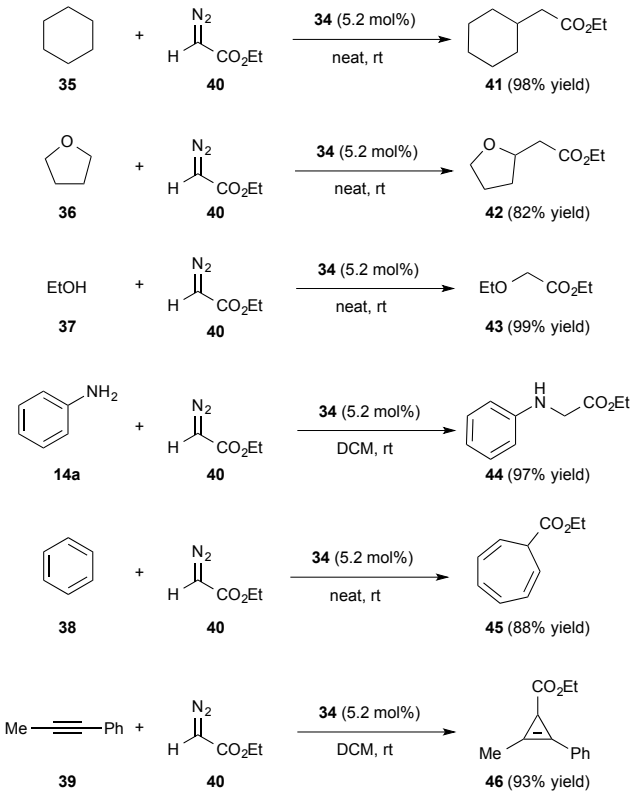


Scheme 17 CuAAC reactions mediated by PS-supported **9h·CuCl**.

Very recently, Díaz-Requejo, Pérez and Pericàs *et al.*[71] reported on the preparation of a fully recyclable heterogenized cationic copper(I) complex **34** and its catalytic performance in carbene transfer reactions[72] both in batch and continuous flow modes. The reaction of PS-supported tris(triazolyl)methyl ether ligand **9h** with $[Cu(MeCN)_4][PF_6]$ led to the formation of the immobilised complex **34** bearing a labile acetonitrile ancillary ligand (Scheme 18). The authors postulated that cationic complex **34** would be much more robust than the neutral counterpart **9h·CuCl**, so that metal leaching during the reactions catalysed by this species could be minimised.



Scheme 18 Preparation of cationic copper(I) complex **34** derived from PS-supported TTM ligand **9h**.



Scheme 19 Carbene transfer reactions catalysed by heterogenized cationic copper(I) complex **34**.

The heterogenized system **34** (5.2 mol%) efficiently catalysed a diverse variety of carbene transfer reactions, under neat conditions or in DCM as solvent at rt, by using inexpensive ethyl diazoacetate (**40**) as the carbene source (Scheme 19).[71] Insertion reactions of the carbene unit into C–H bonds of cyclohexane (**35**) and tetrahydrofuran (**36**), the O–H bond of ethanol (**37**) and the N–H bond of aniline (**14a**), as well as addition reactions to benzene (**38**; Büchner reaction) and 1-phenyl-1-propyne (**39**; cyclopropenation) were all successfully performed giving rise to an array of products (**41**–**46**) in very high yields (82-99% yield). After each carbene transfer reaction, the catalyst was readily separated by simple filtration and reused for next cycle. Importantly, each reaction was repeated five times without significant loss of catalytic activity in each run by using the same sample of supported catalyst. Moreover, twelve consecutive experiments (six different substrates and each experiment run by duplicate) were performed with the same sample of catalyst **34** obtaining comparable yields to those recorded individually.

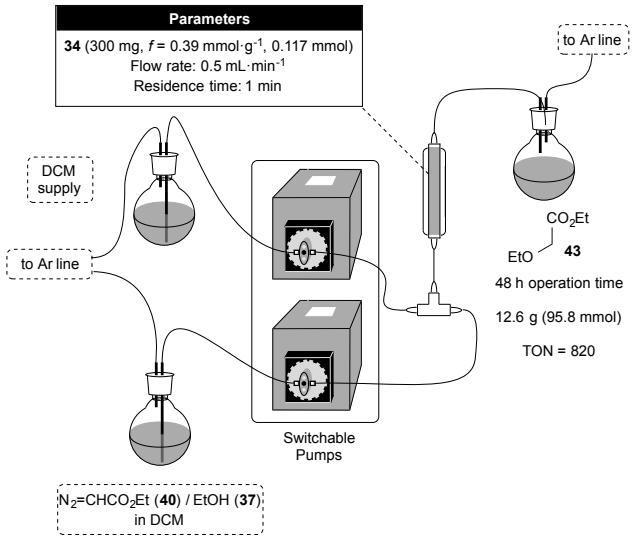


Fig. 6 Experimental setup for continuous flow production of **43** catalysed by **34**.

The application of continuous flow processes[73,74] has recently increased in both industry and academia fields due to their intrinsic

advantages respect to conventional batch processes. The adaptation of covalently heterogenised catalysts to continuous flow processing[73,74] is a relatively new field but it offers several specific advantages: (a) no ligand losses occur during operation as the heterogeneous catalyst is placed in packed-bed reactors, (b) mechanical degradation of the catalyst is suppressed because neither stirring nor shaking is required, and (c) deactivation of the catalyst derived from oxidation and/or hydrolysis of labile catalytic species can be avoided by simply using dry, deoxygenated solvents.

To exploit these advantages, the use in flow of immobilised catalyst **34** for carbene transfer reactions from ethyl diazoacetate (**40**) was implemented.[71] To challenge the catalyst' useful life in flow, the insertion of the carbene derived from **40** into the O–H bond of ethanol (**37**) was studied by using the affordable experimental setup depicted in Fig. 6. After some modification with respect to the batch process, operation of this device at very low catalyst loading led to work with a flow rate as high as 0.5 $mL \cdot min^{-1}$ (equivalent to 1 min residence time). This very stable continuous flow process led to full conversion even after 48 h operation, when the experiment was stopped. When conversion decreased, reconditioning of the catalyst by circulating DCM into the column produced a re-swelling of the polymeric matrix allowing the complete reactivation of the system. In this manner, the process yielded 12.6 g (95.8 mmol, TON = 820) of pure product **43** without any kind of purification. Gratifyingly, copper content analyses showed negligible contamination of the collected samples (0.8–1.6 ppm), indicating the high stability of catalyst **34** under these conditions.

As a further illustration of the potential of **34**, a sequential preparation of five different products (**41**–**44** and **46**) involving four different types of carbene transfers (O–H, N–H and C–H insertions, and cyclopropenation) was successfully carried out taking the advantage of flow processing. Each starting material (**35**–**37**, **14a** and **39**) was circulated for 2 h through the column. Very high productivities, ranging from 2.3 (for **46**) to 17.5 (for **43**) $mmol_{product} \cdot mmol_{Cu}^{-1} \cdot h^{-1}$, were achieved in all cases. The robustness of catalyst **34** was further demonstrated in this experiment, since the same catalyst sample was used to optimise the flow conditions for each substrate and for the synthesis of the whole family of carbene transfer products (Fig. 7).

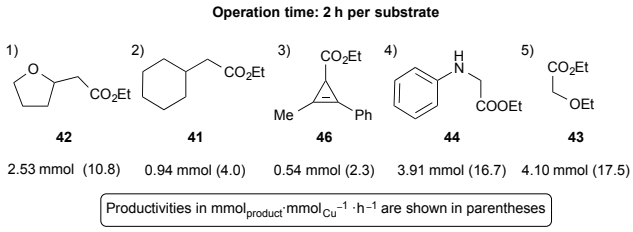
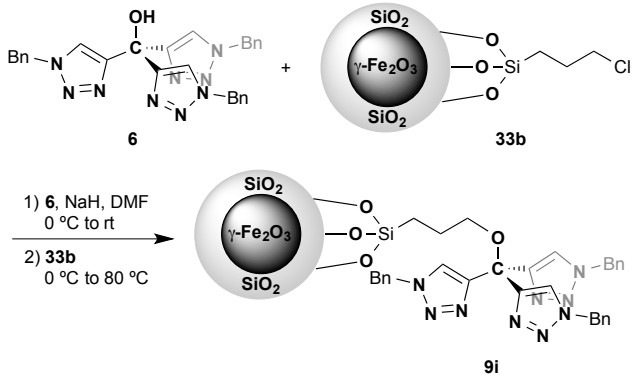


Fig. 7 Sequential production in flow of a small library of compounds resulting from carbene transfer reactions catalysed by **34**.

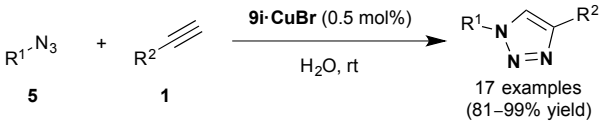
Magnetic nanoparticles (MNPs) have recently arisen as a valuable alternative for the supporting of catalytic species in view of recycling.[75] MNPs can be readily separated from the reaction medium by magnetic decantation. In this way, MNP-supported catalysts are easily recoverable for reuse.

Astruc and co-workers[76] have recently immobilised the tris(triazolyl)methanol **6**[29,34] onto silica-coated iron oxide-based magnetic nanoparticles (γ-Fe_2O_3@SiO_2). These core-shell nanoparticles[77] constitute a class of multifunctional nanostructured materials containing iron oxide nanoparticles as the core and covalently grafted silica as the shell.[78] The anchoring strategy followed by Astruc *et al.* (Scheme 20) relied on the formation of an ether linkage by S_N2-type alkylation reaction of alcohol **6** with 3-chloropropyltris(oxy)silane-functionalised MNPs **33b**, previously prepared through immobilisation of 3-chloropropyltriethoxysilane on the surface of robust γ-Fe_2O_3@SiO_2. The resulting MNP-supported tris(triazolyl)methyl ether ligand **9i** was further used as a stable chelating framework for Cu(I) salts. The corresponding heterogenized copper complexes (**9i·CuCl** and **9i·CuBr**) proved to be highly active and magnetically recoverable TTM-based catalytic systems for CuAAC reactions.[76] The catalytic performance of both MNP-supported systems was evaluated in the model reaction between benzyl azide (**5a**) and phenylacetylene (**1b**) conducted in water[79] at rt under inert atmosphere. Catalyst **9i·CuBr** showed a superior catalytic activity and could be reused up to six times without significant loss of its catalytic activity under these conditions. Analysis of copper leaching after the first cycle confirmed the amount of metal content into the triazole product (**16a**) was negligible (approx. 1.5 pm). In contrast to **6·CuCl** and **9h·CuCl**, however, **9i·CuBr** became readily deactivated in air, probably due to aerobic oxidation into inactive Cu(II) species.



Scheme 20 Anchoring strategy relied on an ether linkage leading to silica-coated iron oxide-based MNP-supported tris(triazolyl)methyl ether ligand **9i**.

The authors applied this methodology to prepare 17 different 1,4-disubstituted 1,2,3-triazoles in very high yields (81–99% yield) repeating each reaction for three times using the same sample of MNP-supported catalyst **9i·CuBr** (Scheme 21).[76] Only a slight decrease in the yield was observed from the first run to the third one. The catalytic performance of **9i·CuBr** tolerated remarkably well a wide range of substrates bearing diverse organic functionalities and all reactions were conducted in water[79] under mild reaction conditions (0.5 mol%, rt). Additionally, applications of complex **9i·CuBr** in three-component processes,[35] involving *in situ* generation of organic azides from benzyl bromides and sodium azide, were also tackled and efficiently delivered triazole products in good to excellent yields.[76]



Scheme 21 CuAAC reactions mediated by MNP-supported **9i·CuBr**.

The same authors[76] used **9i·CuBr** for the preparation of 27-branch dendrimers featuring 1→3 connectivity.[80] Dendritic assemblies containing 9 triazole units[13] and 27 allyl (**47a**) or 27 triethylene glycol (**47b**) termini (Fig. 8) were quantitatively synthesised from a common dendritic nona-azide precursor and two propargyl ether dendrons by using only 8 mol% of **9i·CuBr** per branch (or per CuAAC reaction). The amphiphilic dendrimer **47b** featured by intradendritic triazole rings showcased an impressive accelerating effect in CuAAC reactions acting as a recyclable catalytic nanoreactor at the part-per-million (ppm) level.[81] Interestingly, this water-soluble dendritic nanoreactor (**47b**) was used in turn for its own autocatalysed synthesis.[81]

Most recently,[82] the same laboratory has reported (Scheme 22) the immobilisation of tris(triazolyl)methyl propargyl ether **9c**[37] onto azido-functionalised,[83] silica-coated iron oxide-based magnetic nanoparticles (γ-Fe_2O_3@SiO_2).[77,78] The resulting MNP-supported tris(triazolyl)methyl ether ligand **9j** was further used as a stable chelating framework for Pd species. Complexation reaction of **9j** with $Pd(OAc)_2$ in toluene at 45 ºC led to a immobilised palladium(II) complex [**9j·Pd(OAc)$_2$**], which was used to catalyse the oxidation of benzyl alcohols by air at atmospheric pressure.[82] Analysis of palladium leaching confirmed the amount of metal content into the oxidation product was negligible after four reaction cycles.

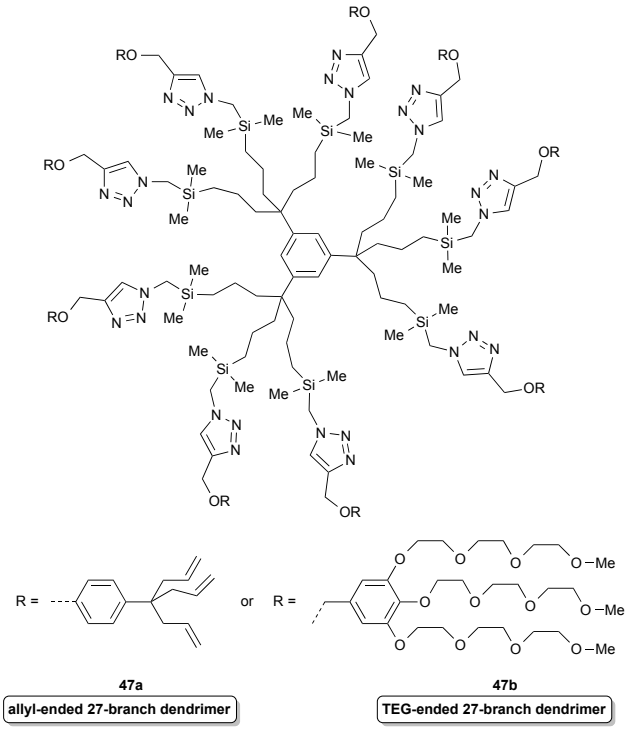
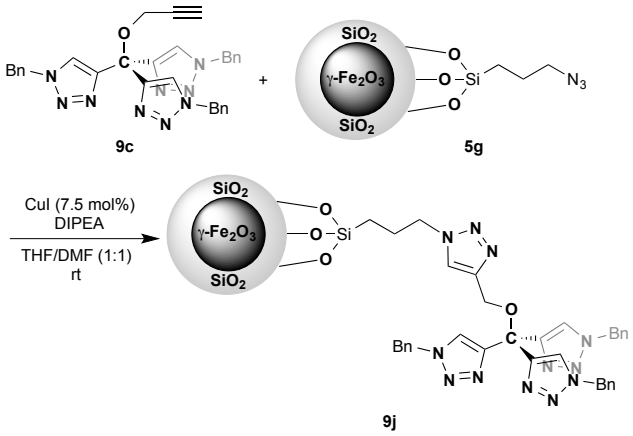
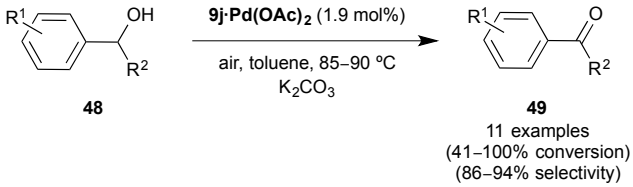


Fig. 8 Dendritic structures containing 9 triazole units and 27 allyl (**47a**) or 27 triethylene glycol (**47b**) termini prepared by CuAAC using **9i·CuBr**.



Scheme 22 Anchoring strategy relied on a triazole linkage leading to silica-coated iron oxide-based MNP-supported tris(triazolyl)methyl ether ligand **9j**.

The authors investigated the substrate scope (11 examples) of the oxidation of primary and secondary alcohols **48** towards the corresponding aldehydes and ketones **49** catalysed by MNP-supported complex **9j·Pd(OAc)$_2$** under the reaction conditions shown in Scheme 23.[82] This transformation proceeded efficiently regardless of the substitution pattern of alcohols **48** and gave good results with both electron-donating and electron-withdrawing substituents. In all cases selectivity towards desired oxidation products **49** was very high, ranging from 86 to 94%.



Scheme 23 Oxidations of benzyl alcohols catalysed by **9j·Pd(OAc)$_2$**.

6. Summary and conclusions

The ready synthetic access to C_3-symmetric tripodal TTM ligands, its favourable geometry for efficient Cu(I) complexation and the derivatisation opportunities offered by the innate OH group present in their structures have favoured the use of these ligands by different laboratories working in very different areas.

Most of the applications developed so far have been in the field of CuAAC reactions and involve the use of a neutral copper(I) complex derived from the benzyl-substituted TTM ligand **6** (**6·CuCl**). It has been found, however, that copper complexes of aryl-substituted TTM ligands (**15a·CuCl** and **15b·CuCl**) are also versatile catalysts suitable for work in a wide variety of solvents. In all these cases, the three-point binding ability provided by these tridentate chelating ligands efficiently stabilises Cu(I) against undesired oxidation and avoids the deactivating complexation of Cu(I) with amino, alcohol or thioether groups present in either reactants or products. This behaviour not only extends catalyst life through favourable self-repair mechanism, but also allows the use of reduced catalyst loadings under mild conditions.

Another group of interesting applications arises from the ready immobilisation of the TTM ligands onto solid supports (PS or MNPs) *via* S_N2 or CuAAC reactions. The corresponding CuX complexes (**9h·CuCl** and **9i·CuBr**) show very high catalytic activity in CuAAC reactions, while the Pd(II) complex [**9j·Pd(OAc)$_2$**] behaves as an active catalyst in Pd-mediated oxidation reactions. In this area, the development of the PS-heterogenized cationic Cu(I) complex (**34**) behaving as a highly active, general catalyst for carbene transfer reactions in batch and flow is remarkable. Catalyst **34** operates with almost complete absence of copper leaching and can be used for prolonged periods of time in processes involving multiple recycling in batch or sequential operation in continuous flow.

The modular design of TTM ligands allows the structural modification of the triazole moieties by simple selection of the organic azide used to build the molecules. These modifications offer potential still to be developed for the modulation of the catalytic performance of the corresponding metal complexes through the modification of steric and electronic properties of the ligand. We anticipate that progress along these lines will lead to the development of efficient, TTM-based catalysts for a variety of metal-mediated processes.

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Notes and references

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