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'Click chemistry' in Cu^{I}-zeolites: a convenient access to glycoconjugates

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ABSTRACT

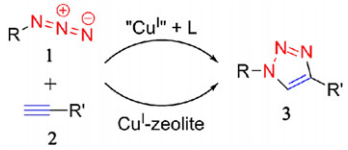
Zeolites modified with Cu^{I} ions are efficient catalyst for 'click' reactions involving carbohydrates and aminoacid derivatives. Glycopeptides and oligosaccharides mimics as well as multivalent carbohydrate derivatives have been obtained in good to high yield using heterogeneous Cu^{I}-modified zeolite catalysts. Contrarily to expectation, pore sizes and internal shapes within zeolites were not a limitation and large glucosyl ditriazoles, disaccharide triazoles, and glucosylated triazolylaminoacids could easily be obtained. Such Cu^{I}-zeolite heterogeneous catalysts greatly facilitated products recovery, through an easy filtration–solvent evaporation sequence, thus offering a convenient alternative to current methods.

1. Introduction

Oligosaccharides and glycopeptides play crucial roles in various key cellular events, such as recognition, immunology, trafficking, signal transduction, etc.[1] Controlled access to these compounds and to their analogs is thus now actively pursued as biological tools, drug candidates, or vaccines.[1,2] Among the methods developed for these purposes, the so-called 'click chemistry',[3] and especially the Cu^{I}-catalyzed version[4] of the Huisgen [3+2]-cycloaddition[5] between terminal alkyne **2** and azide **1**, has become one of the most useful. This 'click' reaction indeed provides a convenient way to connect molecules and to rapidly generate drug-like molecules.[6] Moreover, the 1,4-disubstituted 1,2,3-triazoles **3**, regioselectively produced through this reaction, exhibit similarities to the ubiquitous amide moiety found in nature, but unlike amides, being not susceptible to cleavage.[7] Triazoles are thus considered as peptidic linkage surrogates. Surprisingly, and despite its interest, only a few examples of oligosaccharides and glycopeptides mimics have so far been obtained by 'click chemistry'.[8]

With in mind the goal of providing a mild and easy access to such glycoconjugates, we have applied our recently disclosed heterogeneous version of the Huisgen 'click' reaction[9] to such problems and we reported here our results.

The commonly used protocol for the Huisgen 'click' reaction is based on in situ production of the actual Cu^{I}-catalytic system either from Cu^{II} salts and a reducing agent[4] or from metallic copper or clusters and an oxidizing agent.[10] The inherent instability of Cu^{I} salts has so far limited their use, with nevertheless some exceptions.[4a,11] Cu^{I} salts also induce alkyne homocoupling, diminishing yield, and efficiency, and leading to side-products.[4,12] In sharp contrast, Cu^{I}-modified zeolites offer stabilized Cu^{I} species and avoid the formation of undesirable alkyne homocoupling products (Scheme 1).[9] Cu^{I}-modified zeolites thus appeared as interesting alternatives for a convenient access to oligosaccharides and glycopeptides mimics. Moreover, the inherent heterogeneous nature of such catalysts greatly facilitates product recovery, through simple filtration.



Scheme 1. The Cu^{I}-catalytic systems known to regioselectively promote the Huisgen [3+2]-cycloaddition.

However, pore sizes and internal shapes within zeolites could possibly be a limitation, since molecules have to enter and diffuse within cages or channels 3–8 Å width in order to react (Table 1). Such possible problems could impair the development of this process to large functionalized molecules such as carbohydrates. To alleviate this problem and with glycoconjugate synthesis as goal, we screened several carbohydrates and aminoacids of different sizes and showed here that Cu^{I}-modified zeolites can be applied to such kind of compounds and that they exhibited a surprising flexibility in size. This study also allowed us to look at the selectivity and compatibility with other functional groups of this novel heterogeneous version of 'click chemistry'.

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Table 1
Main structural characteristics of the zeolites used in this study

H-zeolite	Sources	Topology	Pore diameter (Å)	Si/Al ratio	Acidic sites number (mmol/g)
H-USY	Zeolyst International (CBV500)	Cage-type	7.4×7.4	2.8	4.39
H-Y	Aldrich (334413)	Cage-type	7.4×7.4	1.5	6.67
H-β	Zeochem International (ZEOCAT PB/H)	Channel-type	7.6×6.4 5.5×5.5	12.5–17.5	0.90–1.23
H-ZSM5	Zeolyst International (CBV5020)	Channel-type	5.1×5.5 5.3×5.6	15	1.04
H-MOR	Zeolyst International (CBV20A)	Channel-type	6.5×7.0 3.4×3.8	10.3	1.48

2. Results and discussion

2.1. Catalyst and starting materials

H-zeolites mixed with CuCl and heated at 350 °C[13] proved to be the most effective way to prepare the Cu^{I}-modified zeolites used as catalysts in the present study.

Several azides and alkynes derived from carbohydrates and a simple analog were prepared according to known procedures. 2-Azidocyclohexanol **1a**[14] was prepared from the commercially available racemic *trans*-2-aminocyclohexanol by diazo transfer.[15] The glucose or mannose derivatives **1b**, **1d**, and **1f** bearing an azido group at the 6-position were prepared from the corresponding tosylates[16,17] by nucleophilic substitution with sodium azide in DMF. Glucosyl azides **1e** and **1f** were prepared by rearrangement of the corresponding α-thiophenyl mannosides in the presence of sodium azide.[17] The protected propargyl glycosides **2c–d** were prepared using known glycosylations with propargyl alcohol.[18,19]

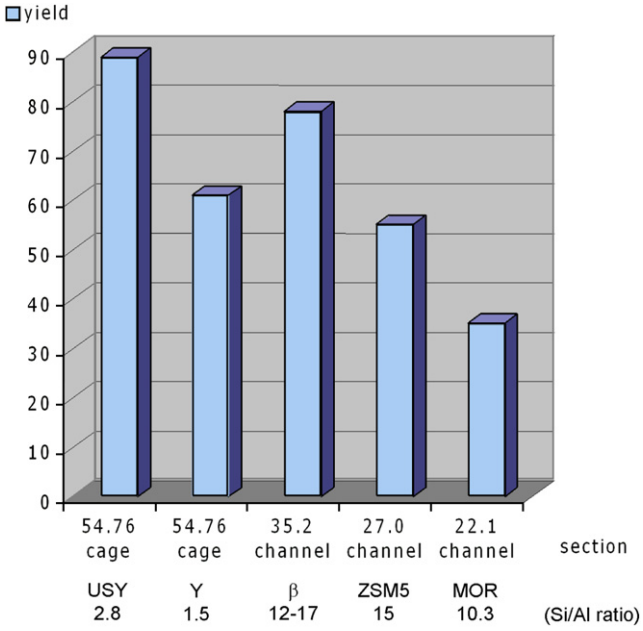
2.2. Conditions optimization

Our preliminary investigations revealed that Cu^{I}-modified USY was the most active catalyst for various derivatives, functionalized but having relatively small sizes.[9] Due to its large pore size, USY should indeed accommodate molecules up to an approximate diameter of 7 Å (Table 1). Nevertheless, we prepared and screened several Cu^{I}-modified zeolites to look for the most appropriate catalyst to have carbohydrate derivatives to react (Table 2).

2-Azidocyclohexanol **1a** was first used as a model, mimicking carbohydrates. This azide and ethylpropiolate were placed in the presence of the Cu^{I}-modified zeolites at room temperature (Table 2). This screening revealed again the efficiency of Cu^{I}-USY, which gave the highest yield of triazole **3a** obtained as a *single* regioisomer (entry 1).

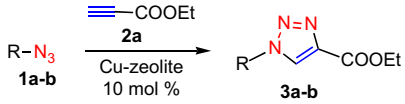
The same screening was then applied to a true carbohydrate, the azide **1b**. Performed at room temperature, the reaction with ethyl propiolate was clearly slow whatever the zeolite catalyst (entry 2). In warm toluene, the reaction readily proceeded giving the expected 1,4-disubstituted triazole **3b** as a single product and Cu^{I}-USY proved again to be the most efficient catalyst (Table 2, entry 3). Other non-polar solvents at lower temperature led to lower conversion and yield (entry 4), while more polar solvents led to lower conversion with some decomposition (entry 5) and even to complete degradation (entry 6).

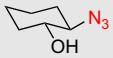
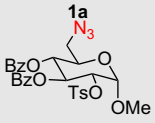
These results clearly showed that heating was required to achieve the Huisgen [3+2]-cycloaddition on large molecules with Cu^{I}-modified zeolites as catalyst, while room temperature was enough for smaller compounds. They also indicated that the zeolite structures have a strong influence on this reaction. Comparing yields with structural parameters of the zeolites used (Table 1) led to two interesting correlations (Scheme 2). From the two cage



Scheme 2. Correlation between yields (%) and zeolite cross-sections (Å^2).

Table 2
Screening of Cu^{I}-modified zeolites and conditions for representative compounds[a,b]



Entry	Azide	Solvent	Temperature (°C)	Time (h)	Cu-USY (%)	Cu-β (%)	Cu-Y (%)	Cu-ZSM5 (%)	Cu-MOR (%)
1	 **1a**	PhMe	20	17	70	58	47	60	66
2		PhMe	20	17	Traces	Traces	Traces	Traces	Traces
3	 **1b**		80	17	89	78	61	55	35
4		CH_2Cl_2	40	17	45[c]	—	—	—	—
5		THF	65	17	45[d]	—	—	—	—
6		MeCN	80	17	Degrad.	—	—	—	—

[a] Yields of isolated pure products.
[b] Cu-zeolite (10%) corresponds to 10 mol % Cu^{I} species based on the theoretical number of native acidic sites of the corresponding H-zeolite.[20]
[c] Compound **1b** (35%) recovered.
[d] Compound **1b** was recovered and decomposition products were formed.

containing zeolites (i.e., Y and USY), the USY zeolite having the largest Si/Al ratio was the more effective. In channel type zeolites (i.e., MOR, ZSM5, and β), the same relationship could be observed, the β-zeolite being the best.

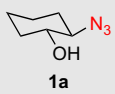
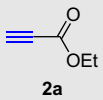
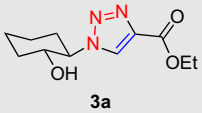
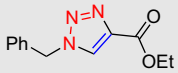
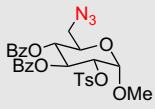
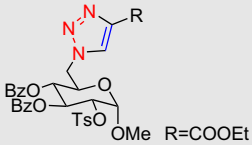
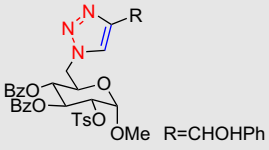
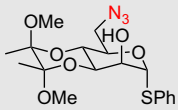
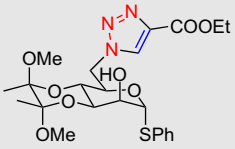
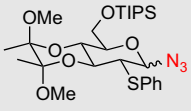
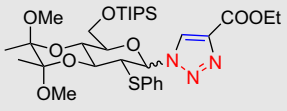
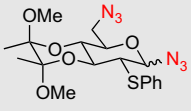
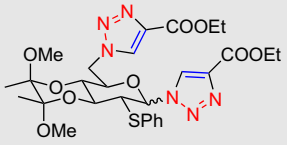
With channel type zeolites, better yields were achieved with the zeolite having the largest cross-section. Moreover, if one except Y zeolite, a clear correlation between cross-section internal size and yield could be observed, suggesting that the reaction takes place *into* the zeolite cages or channels rather that at its external surface, where reagent size would not be a key factor.

2.3. Scope and size limit

With these results in hands and to better delineate any relationship between size and reactivity in Cu^{I}-modified zeolites, we then examined the Cu^{I}-USY catalyzed reaction of azides of increasing sizes derived from carbohydrates (Table 3), as well as the reaction of various alkynes derived from carbohydrates and aminoacids bearing different functional groups (Table 4). For comparison purpose, the reactions of azides **1a**,**b** were reported again in Table 3.

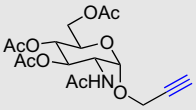
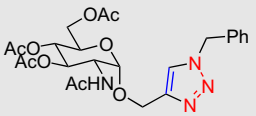
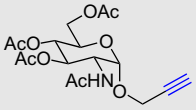
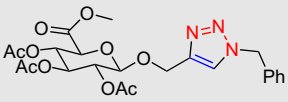
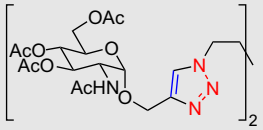
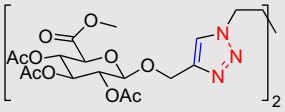
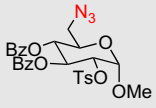
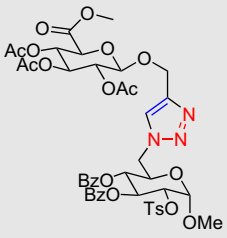
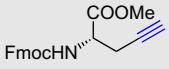
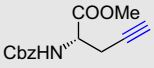
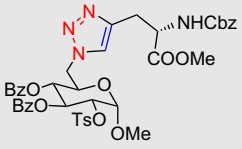
In the presence of Cu^{I}-USY at room temperature, the cyclic azidoalcohol **1a** reacted with ethyl propiolate as other simple azides

Table 3
Cu^{I}-zeolite catalyzed Huisgen [3+2] cycloaddition of azides[a]

Entry	Azide	Alkyne	Adduct	Temperature (°C)	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	20	17	70
2				80	2	96
3	 **1c**	**2a**	 **3c**	20	15	76
4	 **1b**	**2a**	 **3b**	20	72	Traces
5				80	8	89
6	**1b**	 **2b**	 **3d**	20	72	Traces
7				80	8	94
8	 **1d**	**2a**	 **3e**	80	4	97
9	 **1e** (α:β 1:3)	**2a**	 **3f** (α:β 1:3)	80	17	97
10	 **1f** (α:β 3:1)	**2a**	 **3g** (α:β 3:1)	80	17	75

[a] Reaction conditions: Azide **1a**–**f** (1 equiv), alkyne **2a**,**b** (1.2 equiv), solution concentration (0.5 M), 10 mol % of Cu^{I}-USY,[20] toluene.
[b] Yields of isolated pure adduct **3a**–**g** after complete conversion.

Table 4
Cu[I]-zeolite catalyzed Huisgen [3+2] cycloaddition of alkynes[a]

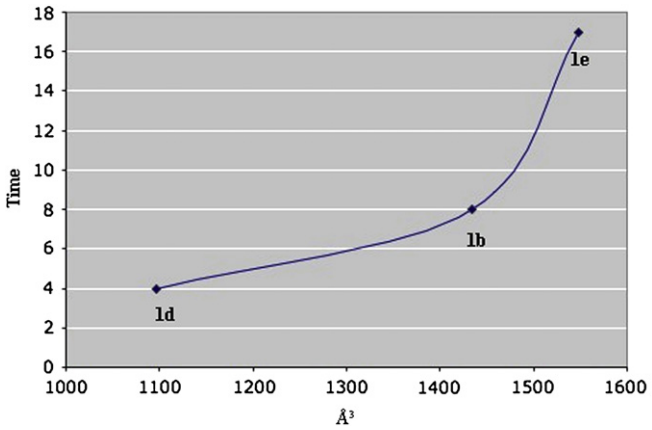
Entry	Azide	Alkyne	Adduct	Temperature (°C)	Time (h)	Yield[b] (%)
1	 **1c**	 **2c**	 **3h**	20	18	76
2	**1c**	 **2d**	 **3i**	20	18	81
3	 **1g**	**2c**[c]	 **3j**	80	16	72
4	**1g**	**2d**[c]	 **3k**	80	16	52
5	 **1b**	**2d**	 **3l**	80	16	79
6	**1b**	 **2e**	—	80	18	0[d]
7	**1b**	 **2f**	 **3m**	80	18	47[e]

[a] Reaction conditions: Azide **1b–g** (1 equiv), alkyne **2c–f** (1.2 equiv), solution concentration (0.5 M), 10 mol % of Cu[I]-USY,[20] toluene.
[b] Yields of isolated pure adduct **3h–m** after complete conversion unless otherwise stated.
[c] Alkyne (2.2 equiv) was used.
[d] The starting carbohydrate was recovered but not the protected aminoacid.
[e] Starting carbohydrate (15%) was also isolated.

such as benzyl azide **1c**, both giving triazoles **3a** and **3c**,[9] respectively, as single regioisomers in good isolated yields (entries 1–3). The yield obtained from **1a** was nevertheless lower than with benzyl azide, despite a slightly longer reaction time, reflecting a lower reactivity of such cyclic secondary azide (entry 1 vs 3). However, at higher temperature, the cycloaddition was faster and almost quantitative yield of the adduct **3a** was obtained in a rapid reaction time (entry 2 vs 1).

Compared to these simple azides, the benzoate and tosylate protected azidoglucoside **1b** did not react at room temperature with different alkynes **2a**,**b** and long mixing times were necessary to detect some adducts formed (entries 4 and 6). However, at 80 °C, the reaction proceeded smoothly, giving the expected adducts as single regioisomers in high yields within 8 h (entries 5 and 7). Prolonging reaction time did not increase further triazole yield (Table 3, entry 5 vs Table 2, entry 3).

The azidomannoside **1d** and the glucosyl azides **1e**,**f** protected with the Ley acetal were selected[17] as a priori more rigid compounds in order to test the ability of such rigid bicyclic systems to penetrate and diffuse into USY cages. To tickle size limit, we also placed on them large groups such as a phenylthio group and even a bulky tri-*iso*propylsilyl group. Indeed, molecular mechanics showed an increasing volume for these carbohydrate derivatives. The phenylthio 6-azido-6-deoxymannoside **1d** reacted faster with ethyl propiolate than the methyl azidoglucoside **1b** and the adduct yield was almost quantitative (entry 8 vs 5). The **1d** volume, determined by molecular mechanics for free molecules, was smaller than the calculated volume of the azidoglucoside **1b** (1097 Å^3 vs 1434 Å^3), with a maximum extended length of 10.7 Å compared to 12.8 Å for **1b**. These results confirmed that the more compact the starting molecule, the easier the reaction.



Scheme 3. Correlation between reaction time (h) and molecular volume (Å^3).

The rigid and bulky 6-*O*-tri-*iso*propylsilyl-2-thiophenyl-2-deoxyglucosyl azide **1e**[17] also quantitatively gave the expected triazole **3f** as a single regioisomer (entry 9 vs 8). Prepared as a mixture of diastereoisomers at the anomeric position, we could expect some discrimination, the α isomer being more compact than the β. However, the anomeric ratio remained unchanged under the reaction conditions. Nevertheless, and as expected, this derivative required a longer reaction time to be fully converted (entry 9 vs 8 vs 5). Indeed, molecular mechanics revealed that the volume of this glucosyl azide **1e** was larger than the one of the azidoglucoside **1b** (1548 Å^3 vs 1434 Å^3) and a clear non-linear correlation between reaction time and molecular volume could be found (Scheme 3). However, electronic effects could not be ruled out since the azido group was at the anomeric position, possibly altering its reactivity.

To distinguish between those effects, the 6-azido-6-deoxy-glucosyl azide **1f** protected again with the Ley acetal was prepared[17] and submitted to the Cu^I-zeolite catalyzed reaction. Looking for some selectivity with this bis-azide, we expected that the primary azide reacted faster than the anomeric one. However, under these conditions, no selectivity was observed and only a single product, the bis-triazole **3g**, could be detected during the course of the reaction. Nevertheless, the reaction time was similar to the preceding bulky **1e** and not to the 'smaller' **1d**, suggesting that the monotriazole could have be first formed at the primary position, leading to a large compound, which then required longer time to be converted to the observed bis-triazole. It is worth noting that in this case also, the anomeric ratio remained unchanged.

After having investigated the behavior of azidoglycosides in our Cu^I-zeolite catalyzed 'click' reaction, we then examined the reactivity of alkynylated glycosides and aminoacids (Table 4). The propargyl α-D-2-acetamido-2-deoxy-3,4,6-*O*-triacetylglucoside **2c**[18] reacted at room temperature with simple azides such as benzyl azide **1c** as any other alkyne derivatives in the presence of Cu^I-zeolite (Table 4, entry 1 vs Table 3, entries 1 and 3). The propargyl β-D-2,3,4-*O*-triacetyl-6-methylglucuronide **2d**[19] exhibited a similar reactivity, giving with the simple azide **1c**, the expected triazole **3i** with similar yield and reaction time (Table 4, entry 2 vs 1).

As an easy access to multivalent carbohydrate systems,[1,21] we tried to connect through two triazole rings two carbohydrate units on a diazido aliphatic chain. The 1,4-diazidobutane was thus prepared[22] and submitted to the propargyl glycosides **2c**,**d**. Both gave the expected triazoles **3j**,**k**, again as single regioisomers, within reaction times similar to those obtained with benzyl azide (entries 3 and 4 vs 1 and 2). As for the glucosyl diazide **1f**, no intermediate could be detected in these reactions. The yield of the corresponding dimeric molecule **3j** obtained from the peracetylated propargyl glucosamine **2c** was similar, although slightly lower, to the one obtained for the bis-triazole **3g** prepared from **1f** (entry 3, Table 4 vs entry 10, Table 3). However, the glucuronic acid derivative **2d** gave a lower yield within the same reaction time (entry 3 vs 4, Table 4). Glucuronic acid derivatives exhibit specific stereoelectronic effect, which lowers their reactivity at the anomeric position in glycosylation reaction.[23] It is thus possible that such effect also affected the reactivity of the corresponding azide. Nevertheless, alkyl azides are known to have a low reactivity and to decompose into nitrogen and amine derivative upon heating,[24] it is thus not so surprising to get lower yield with such alkyldiazide.

With again the same multivalency in mind, but also as a way toward disaccharide mimics, two carbohydrate derivatives were submitted to our 'zeo-click' conditions. The reaction between the azidoglucoside **1b** and the propargyl glucosamine **2c** efficiently gave the disaccharidic triazole **3l** in high yield (entry 5).

As the so-formed glycosylated triazoles **3h–l** represent glycopeptide mimics, we also look for true glycopeptide formation through Cu^I-zeolite catalyzed click reaction. Commercially available protected L-propargylglycine derivatives **2e**,**f** were used as model in reactions with methyl α-D-6-azido-3,4-*O*-benzoyl-6-deoxy-2-*O*-tosylglucoside **1b**. No adduct was produced from the *N*-Fmoc propargylglycine and since only the starting azidoglucoside **1b** was recovered, it seemed that the *N*-Fmoc protecting group decomposed under the reaction conditions (entry 6). In contrast, the *N*-Cbz propargylglycine **2f** proved to be reactive enough and the expected triazole **3m** was isolated in reasonable yield as a single regioisomer, (entry 7). Some starting azidoglucoside **1b** was again recovered, indicating that **2f** may also partially decompose during the reaction.

3. Conclusion

In summary, Cu^I-modified zeolites are able to efficiently catalyze the Huisgen [3+2]-cycloaddition between azides and alkynes derived from carbohydrates and aminoacids. Such heterogeneous catalysts greatly facilitated products recovery, through an easy filtration–solvent evaporation sequence, and good to excellent yields of highly functionalized triazoles were routinely obtained with such Cu^I-zeolite catalysts. This heterogeneous process could thus be extended to carbohydrate and aminoacid azides or alkynes, offering a convenient access toward oligosaccharides, glycopeptides mimics, or multivalent carbohydrate systems. Pore sizes and internal shapes within zeolites was not a limitation, despite the large sizes and volumes of some molecules.

4. Experimental section

4.1. General

Reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F_{254}, Merck) using UV-light and phosphomolybdic acid with Ce^{IV} for visualization. Column chromatographies were performed on silica gel 60 (0.040–0.063 mm, Merck) using mixtures of ethyl acetate and cyclohexane or dichloromethane as eluents. Evaporation of solvents was conducted under reduced pressure at temperatures less than 30 °C unless otherwise noted. Melting points (mp) were measured on a Koffler bench and are uncorrected. IR spectra were recorded with a Perkin–Elmer FTIR 1600 spectrometer (KBr disc) and values are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively. Chemical shifts, δ, and coupling constants J are given in parts per million and hertz, respectively. Chemical shifts δ are reported relative to residual solvent as an internal standard (chloroform-d_1: 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C, methanol-d_5: 3.31 ppm for ^{1}H and 49.0 ppm for ^{13}C). Carbon multiplicities were determined by DEPT 135 experiments. Electrospray (ESI) high-resolution mass spectra (HRMS) were

obtained from the mass spectrometry department of the 'Service Commun d'Analyses', Institut de Chimie, Strasbourg.

Molecular modeling has been performed with Hyperchem Professional Release 7.5. Volumes have been determined using the QSAR properties module after geometry optimization. Geometry optimizations have been computed using MM+ molecular mechanics force field in vacuo with Polar–Ribiere algorithm and rms gradient of 0.001 kcal/(Å mol) as termination condition.

4.2. General procedure for the preparation of Cu^{I}-exchanged zeolite

Cu^{I}-exchanged zeolites were prepared according to a well-established procedure,[13] i.e., heating of a solid mixture of CuCl and H-zeolite (zeolite=USY, Y, ZSM5, MOR, β) in flowing nitrogen at a heating rate of 10 °C/min up to the desired temperature (350 °C).

4.3. Starting materials

4.3.1. Compound *1b*

Obtained by nucleophilic substitution of the corresponding sulfonate (1.5 g, 2.11 mmol, 1 equiv) with sodium azide (206 mg, 3.17 equiv, 1.5 equiv) in DMF (25 mL). After 18 h stirring at 80 °C under argon and evaporation of the solvent under reduced pressure, the white solid was taken off in dichloromethane (25 mL) and washed with distilled water (3×15 mL). The organic layer was dried on sodium sulfate and dichloromethane was evaporated under reduced pressure to give a white solid (1.2 g, 2.06 mmol). Isolated as white solid. Yield 98%. Mp 162–164 °C. $[\alpha]_{589}^{20}$ +10.2 (*c* 1.0, $CHCl_3$). IR (KBr): 2095, 1741, 1713, 1367, 1278, 1252, 1189, 1177, 1166, 1124, 1094, 1041, 1018. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.88–7.82 (m, 2H, Ar Bz–), 7.67–7.62 (m, 2H, Ar Bz–), 7.62–7.57 (m, 2H, Ar Ts–), 7.53–7.44 (m, 2H, Ar Bz–), 7.38–7.32 (m, 2H, Ar Bz–), 7.32–7.27 (m, 2H, Ar Bz–), 6.99–6.91 (m, 2H, Ar Ts–), 5.89 (dd, J_{3-4}=9.9 Hz and J_{3-2}=9.7 Hz, 1H, H_3), 5.32 (dd, J_{4-3}=9.9 Hz and J_{4-5}=9.7 Hz, 1H, H_4), 5.12 (d, J_{1-2}=3.7 Hz, 1H, H_1), 4.60 (dd, J_{2-3}=9.9 Hz and J_{2-1}=3.7 Hz, 1H, H_2), 4.15 (ddd, J_{5-4}=9.7 Hz, J_{5-6a}=5.5 Hz, and J_{5-6b}=3.5 Hz, 1H, H_5), 3.55 (s, 3H, –OMe), 3.40 (d, J_{6a-5}=5.5 Hz, 1H, H_{6a}), 3.39 (d, J_{6b-5}=3.5 Hz, 1H, H_{6b}), 2.21 (s, 3H, $-CH_3$ Ts). ^{13}C NMR ($CDCl_3$, 75 MHz): 165.2 (C=O Bz), 164.9 (C=O Bz), 144.9 (C^{IV} Ts), 133.6 (C^{III} Ar), 133.0 (C^{III} Ar), 132.7 (C^{IV} Ts), 129.8 (C^{III} Ar), 129.7 (C^{III} Ar), 128.8 (C^{IV} Ar), 128.4 (C^{III} Ar), 128.3 (C^{IV} Ar), 128.1 (C^{III} Ar), 127.6 (C^{III} Ar), 97.8 (C_1), 76.5 (C_2), 69.9 (C_4), 69.3 (C_3), 68.8 (C_5), 56.2 ($-OCH_3$), 50.9 (C_6), 21.6 ($-CH_3$ Ts). HRMS (ESI, positive mode) *m*/*z*: calcd for $C_{28}H_{27}N_3O_9SNa$ 604.1360, found 604.1286 $[M+Na]^+$.

4.4. General procedure for the Cu^{I}-zeolite catalyzed [3+2] cycloaddition of azides and terminal alkynes

To a suspension of Cu^{I}-USY (25 mg, 0.1 equiv[17]) in toluene (1 mL) were added azides (0.5 mmol, 1.0 equiv) and then alkynes (0.6 mmol, 1.2 equiv). After 15 h stirring at room temperature or 80 °C, the mixture was taken up in dichloromethane (15 mL) then filtered on nylon membranes (0.20 μm). Solvent evaporation provided the resulting crude product, usually at >95% purity as judged by NMR. Column chromatography was performed when necessary.

4.4.1. Compound *3a*

Obtained using general procedure after 2 h stirring at 80 °C. Isolated as white solid. Yield 96%. Mp 151 °C. IR (KBr): 3141, 2987, 2938, 1894, 2869, 2849, 2357, 2339, 1734, 1719, 1710, 1558, 1553, 1548, 1527, 1452, 1375, 1234, 1219, 1177, 1135, 1127, 1075, 1039, 1024. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.11 (s, 1H, H–triazole ring), 4.36 (q, *J*=7.1 Hz, 2H, $-CH_2CH_3$), 4.19 (ddd, *J*=9.5, 8.1 and 4.0 Hz, 1H, –CH–triazole–), 3.98 (m, 1H, –CHOH–), 3.58 (d, *J*=3.8, 1H, OH), 2.26–2.10 (m, 2H), 2.06–1.82 (m, 3H), 1.52–1.41 (m, 3H), 1.39 (t, *J*=7.1 Hz, 3H, $-CH_2CH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): 160.7, 139.1, 127.5, 72.4, 67.5, 61.2, 34.0, 31.4, 24.6, 24.0, 14.2. HRMS (ESI, positive mode) *m*/*z*: calcd for $C_{11}H_{17}N_3O_3Na$ 262.1162, found 262.1151 $[M+Na]^+$.

4.4.2. Compound *3b*

Obtained using general procedure after 8 h stirring at 80 °C. Isolated as white solid. Yield 89%. Mp 101 °C. $[\alpha]_{589}^{20}$ +30.5 (*c* 1.0, $CHCl_3$). IR (KBr): 3140, 3062, 2928, 2848, 2358, 2340, 1736, 1731, 1715, 1599, 1450, 1371, 1314, 1270, 1190, 1177, 1093, 1055, 1035. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.22 (s, 1H, H–triazole ring), 7.89–7.86 (m, 2H, Ar Bz–), 7.68–7.60 (m, 2H, Ar Bz–), 7.60–7.54 (m, 2H, Ar Ts–), 7.54–7.44 (m, 2H, Ar Bz–), 7.40–7.26 (m, 4H), 7.00–6.90 (m, 2H, Ar Ts–), 5.91 (dd, J_{3-2}=9.9 Hz and J_{3-4}=9.7 Hz, 1H, H_3), 5.22 (dd, J_{4-3}=9.7 Hz and J_{4-5}=9.3 Hz, 1H, H_4), 5.01 (d, J_{1-2}=3.5 Hz, 1H, H_1), 4.73–4.69 (m, 1H, H_5), 4.60 (dd, J_{2-3}=9.9 Hz and J_{2-1}=3.6 Hz, 1H, H_2), 4.51–4.40 (m, 2H, H_6), 4.41 (q, *J*=7.1 Hz, 2H, $-CH_2CH_3$), 3.18 (s, 3H, $-OCH_3$), 2.20 (s, 3H, $-CH_3$ Ts–), 1.41 (t, *J*=7.1 Hz, 3H, $-CH_2CH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): 165.5 (C=O Bz), 164.8 (C=O Bz), 160.6 (C=O ester), 145.0 (C^{IV} Ts), 140.3 (C^{IV} triazole), 133.9 (C^{III} Ar), 133.1 (C^{III} Ar), 132.6 (C^{IV} Ts), 129.9 (C^{III} triazole), 129.7 (C^{III} Ar), 129.6 (C^{III} Ar), 129.1 (C^{III} Ar), 128.6 (C^{IV} Ar), 128.5 (C^{III} Ar), 128.1 (C^{III} Ar), 127.9 (C^{IV} Ar), 127.5 (C^{III} Ar), 97.7 (C_1), 76.1 (C_2), 70.4 (C_4), 69.0 (C_3), 67.8 (C_5), 61.4 ($-CH_2CH_3$), 56.1 ($-OCH_3$), 51.1 (C_6), 21.6 ($-CH_3$ Ts), 14.3 ($-CH_2CH_3$). HRMS (ESI, positive mode) *m*/*z*: calcd for $C_{33}H_{34}N_3O_{11}SNa$ 702.1728, found 702.1762 $[M+Na]^+$.

4.4.3. Compound *3d*

Obtained using general procedure after 8 h stirring at 80 °C. Isolated as white solid, mixture of diastereoisomers (i.e., *dia1* and *dia2*) in a 1:1 ratio. Yield 94%. Mp 168–172 °C. IR (KBr): 3431, 3120, 3031, 3000, 2925, 2838, 2361, 2341, 1730, 1599, 1494, 1450, 1376, 1314, 1273, 1189, 1179, 1129, 1090, 1031. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.88–7.84 (m, 2H, Ar Bz–), 7.66–7.59 (m, 2H, Ar Bz–), 7.56 (m, 2H, Ar Ts–), 7.53–7.44 (m, 2H, Ar Bz–), 7.43–7.26 (m, 9H, Ar Bz–+Ar –CHOHPh+H–triazole ring), 6.95–6.93 (m, 2H, Ar Ts–), 6.04 (d, *J*=3.1 Hz, 0.5H, –CHOH–(*dia1*)), 6.00 (d, *J*=3.5 Hz, 0.5H, –CHOH–(*dia2*)), 5.87 (t, *J*=9.7 Hz, 0.5H, H_3–(*dia1*)), 5.86 (t, *J*=9.7 Hz, 0.5H, H_3–(*dia2*)), 5.20 (dd, J_{4-3}=9.7 Hz and J_{4-5}=9.5 Hz, 1H, H_4), 4.98 (d, J_{1-2}=3.7 Hz, 0.5H, H_1–(*dia1*)), 4.97 (d, J_{1-2}=3.7 Hz, 0.5H, H_1–(*dia2*)), 4.66–4.50 (m, 2H, H_2+H_5), 4.42–4.23 (m, 2H, H_6), 3.11 (s, 1.5H, $-OCH_3$–(*dia1*)), 3.04 (s, 1.5H, $-OCH_3$–(*dia2*)), 2.20 (s, 3H, $-CH_3$ Ts). ^{13}C NMR ($CDCl_3$, 75 MHz): 165.5 (C=O Bz), 164.8 (C=O Bz), 144.9 (C^{IV} Ts), 142.0 (C^{IV} triazole), 133.8 (C^{III} Ar), 133.1 (C^{III} Ar), 132.6 (C^{IV} Ts), 129.9 (C^{III} triazole), 129.7 (C^{III} Ar), 128.6 (C^{IV} Ar), 128.5 (C^{III} Ar), 128.4 (C^{III} Ar), 128.1 (C^{III} Ar), 128.0 (C^{III} Ar), 127.5 (C^{III} Ar), 126.3 (C^{III} Ar), 126.1 (C^{III} Ar), 97.6 (C_1), 76.2 (C_2), 70.4 (C_4), 69.1 (C_3), 68.2 (C_5), 55.9 ($-OCH_3$), 55.8 (–CHOH–), 50.8 (C_6), 21.6 ($-CH_3$ Ts). HRMS (ESI, positive mode) *m*/*z*: calcd for $C_{37}H_{36}N_3O_{11}SNa$ 736.1935, found 736.2018 $[M+Na]^+$.

4.4.4. Compound *3e*

Obtained using general procedure after 4 h stirring at 80 °C. Isolated as white solid. Yield 97%. Mp 173 °C. $[\alpha]_{589}^{20}$ +154.1 (*c* 1.0, $CHCl_3$). IR (KBr): 3455, 3150, 2987, 2943, 2921, 2834, 2364, 1725, 1552, 1470, 1443, 1392, 1377, 1351, 1208, 1129, 1079, 1066, 1048. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.92 (s, 1H, H–triazole ring), 7.17–7.12 (m, 5H, Ar PhS–), 5,53 (d, J_{1-2}=0.5 Hz, 1H, H_1), 4.84 (dd, J_{6a-6b}=13.7 Hz and J_{6a-5}=1.7 Hz, 1H, H_{6a}), 4.56–4.40 (m, 2H, H_{6b}+H_5), 4.37 (q, J=7.1 Hz, 2H, $-CH_2CH_3$), 4.18 (d, J_{2-3}=2.2 Hz, 1H, H_2), 4.02 (dd, J_{3-4}=9.9 Hz and J_{3-2}=2.9 Hz, 1H, H_3), 3.91 (dd, J_{4-3}=9.9 Hz and J_{4-5}=9.7 Hz, 1H, H_4), 3.27 (s, 3H, $-OCH_3$), 3.17 (s, 3H, $-OCH_3$), 3.08 (br s, 1H, –OH), 1.37 (t, J=7.1 Hz, 3H, $-CH_2CH_3$), 1.30 (s, 3H, $-CH_3$), 1.29 (s, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): 160.5 (C=O ester), 140.0 (C^{IV} triazole), 132.0 (C^{III} Ar PhS–), 131.9 (C^{IV} Ar PhS–), 129.1 (C^{III} triazole), 128.9 (C^{III} Ar), 127.8 (C^{III} Ar PhS–), 100.5 (C^{IV} Ley acetal), 100.2 (C^{IV} Ley acetal), 87.8 (C_1), 70.5 (C_3), 69.7 (C_2), 68.2 (C_4),

64.4 (C_5), 61.0 (–CH_2CH_3), 50.2 (C_6), 48.1 (–OCH_3), 17.6 (–CH_3), 17.5 (–CH_3), 14.3 (–CH_2CH_3). HRMS (ESI, positive mode) *m*/*z*: calcd for $C_{23}H_{31}N_3O_8SNa$ 532.1877, found 532.1860 $[M+Na]^+$.

4.4.5. Compound **3f**

Obtained using general procedure after 17 h stirring at 80 °C. Isolated as white solid, mixture of α/β isomers in a 1:3 ratio. Yield 97%. Mp (dec) 196–198 °C. IR (KBr): 3129, 2934, 2863, 2353, 2334, 1717, 1709, 1559, 1553, 1472, 1464, 1458, 1447, 1398, 1387, 1377, 1363, 1332, 1316, 1265, 1252, 1220, 1142, 1081, 1044. β Isomer (major): ^{1}H NMR ($CDCl_3$, 300 MHz): 7.64 (s, 1H, H–triazole ring), 7.22–7.07 (m, 5H, Ar PhS–), 5.82 (d, J_{1-2}=9.9 Hz, 1H, H_1), 4.36 (q, *J*=7.1 Hz, 2H, –CH_2CH_3), 4.04 (dd, J_{4-5}=9.7 Hz and J_{4-3}=9.5 Hz, 1H, H_4), 3.93 (d, J_{6a-5}=2.9 Hz, 1H, H_{6a}), 3.91 (d, J_{6b-5}=2.2 Hz, 1H, H_{6b}), 3.85 (dd, J_{3-2}=11.3 Hz and J_{3-4}=9.5 Hz, 1H, H_3), 3.66 (ddd, J_{5-4}=9.9 Hz, J_{5-6a}=2.8 Hz and J_{5-6b}=2.5 Hz, 1H, H_5), 3.53 (dd, J_{2-3}=11.3 Hz and J_{2-1}=9.9 Hz, 1H, H_2), 3.40 (s, 3H, –OCH_3), 3.33 (s, 3H, –O CH_3), 1.42 (s, 3H, –CH_3), 1.38 (t, J=7.1 Hz, 3H, –CH_2CH_3), 1.35 (s, 3H, –CH_3), 1.03–0.89 (m, 21H, –Si^{i}Pr$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): 160.1 (C=O ester), 139.9 (C^{IV} triazole), 133.6 (C^{III} Ar PhS–), 131.9 (C^{IV} Ar PhS–), 128.9 (C^{III} Ar PhS–), 128.0 (C^{III} Ar PhS–), 125.7 (C^{III} triazole), 100.6 (C^{IV} Ley acetal), 99.9 (C^{IV} Ley acetal), 89.8 (C_1), 77.8 (C_5), 70.4 (C_3), 66.3 (C_4), 61.1 (–CH_2CH_3), 60.7 (C_6), 54.7 (C_2), 48.4 (–OCH_3), 48.2 (–OCH_3), 17.9 (2C^{III}, –*C*H of –Si^{i}Pr$_3$), 17.7 (C^{III}, –*C*H of –Si^{i}Pr$_3$), 17.7 (–CH_3), 17.6 (–CH_3), 14.3 (–CH_2CH_3), 11.9 (6C^I, –CH_3 of –Si^{i}Pr$_3$). HRMS (ESI, positive mode) *m*/*z*: calcd for $C_{32}H_{51}N_3O_8SSiNa$ 688.3058, found 688.3023 $[M+Na]^+$.

4.4.6. Compound **3g**

Obtained using general procedure after 17 h stirring at 80 °C. Isolated as white solid, mixture of α/β isomers in a 3:1 ratio. Yield 75%. Mp 171–174 °C. IR (KBr): 3155, 2921, 2849, 2358, 2342, 1729, 1457, 1436, 1429, 1398, 1386, 1376, 1346, 1207, 1179, 1123, 1034. α Isomer (major): ^{1}H NMR ($CDCl_3$, 300 MHz): 8.09 (s, 1H, H–triazole ring), 8.08 (s, 1H, H–triazole ring), 7.40 (m, 2H, Ar PhS–), 7.28 (m, 3H, Ar PhS–), 6.07 (d, *J*=5.9 Hz, 1H, H_1), 4.90 (dd, J_{6a-6b}=12.2 Hz and J_{6a-5}=9.3 Hz, 1H, H_{6a}), 4.85 (dd, J_{6b-6a}=12.3 Hz and J_{6b-5}=5.1 Hz, 1H, H_{6b}), 4.50–4.38 (m, 6H, 2×–CH_2CH_3+H_3+H_5), 3.68 (dd, J_{2-3}= 12.1 Hz and J_{2-1}=5.9 Hz, 1H, H_2), 3.53 (dd, J_{4-5}=9.8 Hz and J_{4-3}= 9.7 Hz, 1H, H_4), 3.36 (s, 3H, –OCH_3), 3.30 (s, 3H, –OCH_3), 1.44 (t, *J*=7.1 Hz, 3H, –CH_2CH_3), 1.40 (t, *J*=7.1 Hz, 3H, –CH_2CH_3), 1.38 (s, 3H, –CH_3), 1.34 (s, 3H, –CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): 160.7 (C=O ester), 160.4 (C=O ester), 140.4 (C^{IV} triazole), 139.7 (C^{IV} triazole), 133.5 (C^{IV} Ar PhS–), 132.6 (C^{III} Ar PhS–), 129.7 (C^{III} Ar PhS–), 129.0 (C^{III} triazole), 128.8 (C^{III} triazole), 128.1 (C^{III} Ar PhS–), 100.6 (C^{IV} Ley acetal), 85.7 (C_1), 71.9 (C_5), 68.2 (C_3), 67.4 (C_4), 61.5 (–CH_2CH_3), 61.4 (–CH_2CH_3), 51.3 (C_2), 49.3 (C_6), 49.0 (–OCH_3), 48.1 (–OCH_3), 17.6 (–CH_3), 17.5 (–CH_3), 14.3 (2×–CH_2CH_3). HRMS (ESI, positive mode) *m*/*z*: calcd for $C_{28}H_{36}N_6O_9SNa$ 655.2157, found 655.2153 $[M+Na]^+$.

4.4.7. Compound **3h**

Obtained using general procedure after 18 h stirring at 20 °C. Isolated as white solid. Yield 76%. Mp 55 °C. $[\alpha]_{589}^{20}$ +68.1 (*c* 1.0, $CHCl_3$). IR (KBr): 2928, 1738, 1664, 1455, 1422, 1366, 1219, 1119, 1033, 1012. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.03 (s, 1H, H–triazole ring), 7.45–7.27 (m, 5H, Ar Ph–), 5.61 (s, 2H, –CH_2Ph), 5.22 (dd, J_{3-2}=11.0 Hz and J_{3-4}=10.2 Hz, 1H, H_3), 5.01 (dd, J_{4-3}=10.1 Hz and J_{4-5}=9.9 Hz, 1H, H_4), 4.91 (d, J_{1-2}=3.7 Hz, 1H, H_2), 4.81 (d, *J*=12.4 Hz, 1H, –OCH_2–triazole), 4.68 (d, *J*=12.4 Hz, 1H, –OCH_2–triazole), 4.24 (dd, J_{2-3}=11.0 Hz and J_{2-1}=3.7 Hz, 1H, H_2), 4.21 (dd, J_{6a-6b}=12.4 Hz and *J*=4.2 Hz, 1H, H_{6a}), 4.05–3.95 (m, 2H, H_5+H_{6b}), 2.04 (s, 3H, –OAc), 1.99 (s, 3H, –OAc), 1.94 (s, 3H, –OAc), 1.85 (s, 3H, –NHAc). ^{13}C NMR ($CDCl_3$, 75 MHz): 173.5 (C=O acetamide), 172.3 (C=O acetate), 172.0 (C=O acetate), 171.2 (C=O acetate), 145.2 (C^{IV} triazole), 136.7 (C^{IV} Ar Ph–), 130.1 (C^{III} Ar Ph–), 129.7 (C^{III} Ar Ph–), 129.2 (C^{III} Ar Ph–), 125.3 (C^{III} triazole), 98.1 (C_1), 72.2 (C_3), 70.1 (C_5), 69.1 (C_4), 63.1 (–OCH_2–triazole), 61.8 (C_6), 55.0 (–CH_2Ph), 52.8 (C2) 22.4 (–CH_3 of –NHAc), 20.6 (–CH_3 of –OAc), 20.5 (–CH_3 of –OAc), 20.5 (–CH_3 of –OAc). HRMS (ESI, positive mode) *m*/*z*: calcd for $C_{24}H_{30}N_4O_9Na$ 541.1905, found 541.1913 $[M+Na]^+$.

4.4.8. Compound **3i**

Obtained using general procedure after 18 h stirring at 20 °C. Isolated as white solid. Yield 81%. Mp 140 °C. $[\alpha]_{589}^{20}$ −53.3 (*c* 1.0, $CHCl_3$). IR (KBr): 3142, 2957, 1743, 1499, 1455, 1436, 1369, 1325, 1220, 1158, 1128, 1092, 1039. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.46 (s, 1H, H–triazole ring), 7.33–7.19 (m, 5H, Ar Ph–), 5.46 (s, 2H, –CH_2Ph), 5.18–5.10 (m, 2H, H_3+H_4), 4.92 (dd, J_{2-3}=8.4 Hz and J_{2-1}=7.7 Hz, 1H, H_2), 4.84 (d, *J*=12.7 Hz, 1H, –OCH_2–triazole), 4.75 (d, *J*=12.7 Hz, 1H, –OCH_2–triazole), 4.66 (d, J_{1-2}=7.7 Hz, 1H, H_1), 4.02 (d, J_{5-4}=9.1 Hz, 1H, H_5), 3.66 (s, 3H, –OCH_3), 1.96 (s, 3H, –OAc), 1.93 (s, 3H, –OAc), 1.79 (s, 3H, –OAc). ^{13}C NMR ($CDCl_3$, 75 MHz): 169.8 (C=O acetate), 169.2 (C=O acetate), 169.0 (C=O acetate), 167.0 (C=O methyl ester), 144.2 (C^{IV} triazole), 134.4 (C^{IV} Ar Ph–), 128.9 (C^{III} Ar Ph–), 128.6 (C^{III} Ar Ph–), 127.9 (C^{III} Ar Ph–), 122.8 (C^{III} triazole), 99.5 (C_1), 72.2 (C_2), 71.7 (C_3), 70.9 (C_5), 69.1 (C_4), 62.8 (–OCH_2–triazole), 53.9 (–OCH_3), 52.6 (–CH_2Ph), 20.4 (–CH_3 of –OAc), 20.3 (–CH_3 of –OAc). HRMS (ESI, positive mode) *m*/*z*: calcd for $C_{23}H_{27}N_3O_{10}Na$ 528.1589, found 528.1834 $[M+Na]^+$.

4.4.9. Compound **3j**

Obtained using general procedure after 16 h stirring at 80 °C. Isolated as white solid. Yield 72%. Mp 88–92 °C. $[\alpha]_{589}^{20}$ +51.8 (*c* 0.8, $CHCl_3$). IR (KBr): 3296, 2927, 2857, 1738, 1662, 1537, 1436, 1367, 1220, 1120, 1029. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.57 (s, 2H, H–triazole ring), 6.09 (d, *J*=9.3 Hz, 2H, NH), 5.18 (dd, J_{3-2}=10.2 Hz and J_{3-4}= 9.7 Hz, 2H, H_3), 5.08 (dd, J_{4-3}=9.7 Hz and J_{4-5}=9.5 Hz, 2H, H_4), 4.87 (d, J_{1-2}=3.7 Hz, 2H, H_1), 4.79 (d, *J*=12.4 Hz, 2H, –OCH_2–triazole), 4.61 (d, *J*=12.4 Hz, 2H, –OCH_2–triazole), 4.45–4.27 (m, 6H, triazole–CH_2CH_2–+H_2), 4.24–4.15 (dd, J_{6a-6b}=12.4 Hz and J_{6a-5}=4.2 Hz, 2H, H_{6a}), 4.09–3.92 (m, 4H, H_5+H_{6b}), 2.05 (s, 6H, –OAc), 2.01–1.89 (m, 16H, 2×–OAc+triazole–CH_2CH_2–), 1.87 (s, 6H, –NHAc). ^{13}C NMR ($CDCl_3$, 75 MHz): 171.1 (C=O acetate), 170.6 (C=O acetate), 170.2 (C=O acetate), 169.2 (C=O acetamide), 143.4 (C^{IV} triazole), 143.2 (C^{IV} triazole), 122.9 (C^{III} triazole), 96.5 (C_1), 70.9 (C_3), 68.1 (C_5), 67.9 (C_4), 61.8 (–OCH_2–triazole), 60.8 (C_6), 51.6 (C_2), 49.3 (triazole–CH_2CH_2–), 27.0 (triazole–CH_2CH_2–), 23.0 (–CH_3 of –NHAc), 20.6 (–CH_3 of –OAc), 20.6 (–CH_3 of –OAc), 20.5 (–CH_3 of –OAc). HRMS (ESI, positive mode) *m*/*z*: calcd for $C_{38}H_{54}N_8O_{18}Li$ 917.3711, found 917.3592 $[M+Li]^+$.

4.4.10. Compound **3k**

Obtained using general procedure after 16 h stirring at 80 °C. Isolated as white solid. Yield 52%. Mp 152–155 °C. $[\alpha]_{589}^{20}$ −37.3 (*c* 1.0, $CHCl_3$). IR (KBr): 2926, 2338, 1756, 1717, 1713, 1472, 1464, 1458, 1436, 1419, 1387, 1375, 1228, 1157, 1045. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.59 (s, 2H, H–triazole ring), 5.31–5.16 (m, 4H, H_3+H_4), 5.00 (dd, J_{2-3}=9.1 Hz and J_{2-1}=7.5 Hz, 2H, H_2), 4.93 (d, *J*=12.6 Hz, 2H, –OCH_2–triazole), 4.83 (d, *J*=12.6 Hz, 2H, –OCH_2–triazole), 4.73 (d, J_{1-2}=7.5 Hz, 2H, H_1), 4.37 (br s, 4H, triazole–CH_2CH_2–), 4.08 (d, J_{5-4}=9.3 Hz, 2H, H_5), 3.73 (s, 6H, –OCH_3), 2.02 (s, 6H, –OAc), 2.00 (s, 6H, –OAc), 1.98 (s, 6H, –OAc), 1.96–1.89 (m, 4H, triazole–CH_2CH_2–). ^{13}C NMR ($CDCl_3$, 75 MHz): 170.0 (C=O acetate), 169.4 (C=O acetate), 169.3 (C=O acetate), 167.3 (C=O methyl ester), 144.3 (C^{IV} triazole), 123.1 (C^{III} triazole), 100.0 (C_1), 72.4 (C_2), 71.9 (C_3), 71.2 (C_5), 69.3 (C_4), 63.3 (–OCH_2–triazole), 52.9 (–OCH_3), 49.3 (triazole–CH_2CH_2–), 27.0 (triazole–CH_2CH_2–), 20.6 (–CH_3 of –OAc), 20.6 (–CH_3 of –OAc), 20.5 (–CH_3 of –OAc). HRMS (ESI, positive mode) *m*/*z*: calcd for $C_{36}H_{48}N_6O_{20}Na$ 907.2816, found 907.2922 $[M+Na]^+$.

4.4.11. Compound **3l**

Obtained using general procedure after 16 h stirring at 80 °C. Isolated as white solid. Yield 79%. Mp 174 °C. $[\alpha]_{589}^{20}$ −0.6 (*c* 1.0,

$CHCl_3$). IR (KBr): 2957, 2926, 2852, 1742, 1600, 1492, 1450, 1371, 1314, 1276, 1232, 1221, 1206, 1189, 1178, 1158, 1133, 1094, 1070, 1050, 1034, 1011. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.91–7.80 (m, 2H, Ar Bz–), 7.70 (s, 1H, H–triazole ring), 7.66–7.60 (m, 2H, Ar Bz–), 7.60–7.53 (m, 2H, Ar Ts–), 7.53–7.42 (m, 2H, Ar Bz–), 7.39–7.22 (m, 4H, Ar Bz–), 6.99–6.89 (m, 2H, Ar Ts–), 5.89 (dd, J_{3-2}=9.9 Hz and J_{3-4}=9.7 Hz, 1H, H_3), 5.29–5.15 (m, 3H, H_4+$H_{3'}$+$H_{4'}$), 5.05–4.96 (m, 2H, H_1+$H_{2'}$), 4.94 (d, J=12.6 Hz, –OCH_2–triazole), 4.78 (d, J=12.6 Hz, –OCH_2–triazole), 4.70 (d, $J_{1'-2'}$=7.7 Hz, $H_{1'}$), 4.66–4.55 (m, 2H, H_2+H_5), 4.47–4.33 (m, 2H, H_6), 4.13–4.01 (m, 1H, $H_{5'}$), 3.75 (s, 3H, –OMe), 3.18 (s, 3H, –OCH_3), 2.19 (s, 3H, –CH_3 Ts–), 2.01 (s, 3H, –OAc), 2.00 (s, 3H, –OAc), 1.98 (s, 3H, –OAc). ^{13}C NMR ($CDCl_3$, 75 MHz): 169.9 (C=O acetate), 169.3 (C=O acetate), 169.1 (C=O acetate), 167.1 (C=O methyl ester), 165.4 (C=O ester Bz–), 164.7 (C=O ester Bz–), 144.9 (C^{IV} Ts), 144.0 (C^{IV} triazole), 133.8 (C^{III} Ar), 133.1 (C^{III} Ar), 132.6 (C^{IV} Ts), 129.8 (C^{III} Ar), 129.7 (C^{III} Ar), 129.6 (C^{III} Ar), 128.6 (C^{IV} Ar), 128.4 (C^{III} Ar), 128.0 (C^{III} Ar), 127.5 (C^{III} Ar), 124.5 (C^{III} triazole), 99.8 ($C_{1'}$), 97.5 (C_1), 76.2 (C_2), 72.4 ($C_{2'}$), 71.8 ($C_{3'}$), 71.1 ($C_{5'}$), 70.4 (C_4), 69.2 ($C_{4'}$), 69.1 (C_3), 68.0 (C_5), 63.0 (–OCH_2–triazole), 55.9 (–OCH_3), 52.8 (–COOCH_3), 50.7 (C_6), 21.5 (–CH_3 of Ts), 20.5 (–CH_3 of –OAc), 20.5 (–CH_3 of –OAc), 20.4 (–CH_3 of –OAc). HRMS (ESI, positive mode) m/z: calcd for $C_{44}H_{47}N_3O_{19}$SNa 976.2417, found 976.2398 $[M+Na]^+$.

4.4.12. Compound **3m**

Obtained using general procedure after 18 h stirring at 80 °C. Isolated as white solid. Yield 47%. Mp 112 °C. $[\alpha]_{589}^{20}$ +10.5 (c 0.4, $CHCl_3$). IR (KBr): 3367, 2921, 2850, 2106, 1722, 1600, 1518, 1452, 1367, 1315, 1265, 1214, 1191, 1176, 1129, 1092. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.91–7.82 (m, 2H, Ar Bz–), 7.67–7.60 (m, 2H, Ar Bz–), 7.60–7.55 (m, 2H, Ar Ts–), 7.54–7.42 (m, 3H, Ar Bz–), 7.41–7.26 (m, 9H, 5Ar Bn–+4Ar Bz–), 6.97–6.90 (m, 2H, Ar Ts–), 5.88 (dd, J_{3-2}=9.9 Hz and J_{3-4}=9.7 Hz, 1H, H_3), 5.72 (d, J=7.8 Hz, 1H, –NH–), 5.15 (dd, J_{4-3}=9.7 Hz and J_{4-5}=9.5 Hz, 1H, H_4), 5.12 (s, 2H, –CH_2Ph), 5.01 (d, J_{1-2}=3.6 Hz, 1H, H_1), 4.73–4.65 (m, 1H, H_5), 4.65–4.60 (dd, J_{2-3}=9.9 Hz and J_{2-1}=3.6 Hz, 1H, H_2), 4.60–4.53 (m, 1H, H glycine), 4.44–4.32 (m, 2H, H_6), 3.74 (s, 3H, –OCH_3), 3.33–3.23 (m, 2H, –CH_2–glycine), 3.19 (s, 3H, –COOMe), 2.19 (s, 3H, –CH_3 Ts). ^{13}C NMR ($CDCl_3$, 100 MHz): 171.5 (C=O ester), 165.4 (C=O ester Bz–), 164.8 (C=O ester Bz–), 155.8 (C=O Cbz), 144.9 (C^{IV} Ts), 140.6 (C^{IV} triazole), 136.2 (C^{IV} Cbz), 133.8 (C^{III} Ar), 133.1 (C^{III} Ar), 132.8 (C^{IV} Ts), 129.9 (C^{III} Ar), 129.8 (C^{III} Ar), 129.7 (C^{III} Ar), 128.7 (C^{IV} Ar), 128.5 (C^{III} Ar), 128.5 (C^{III} Ar), 128.2 (C^{III} Ar), 128.1 (C^{III} Ar), 127.6 (C^{III} Ar), 123.6 (C^{III} triazole), 97.8 (C_1), 76.3 (C_2), 70.3 (C_4), 69.2 (C_3), 68.0 (C_5), 67.0 (C^{II} Cbz), 56.0 (–OCH_3), 53.5 (C^{III} glycine), 52.6 (–COOCH_3), 50.7 (C_6), 28.2 (–CH_2–glycine), 21.6 (–CH_3 Ts). HRMS (ESI, positive mode) m/z: calcd for $C_{42}H_{42}N_4O_{13}$SNa 865.2361, found 865.2360 $[M+Na]^+$.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.086.

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