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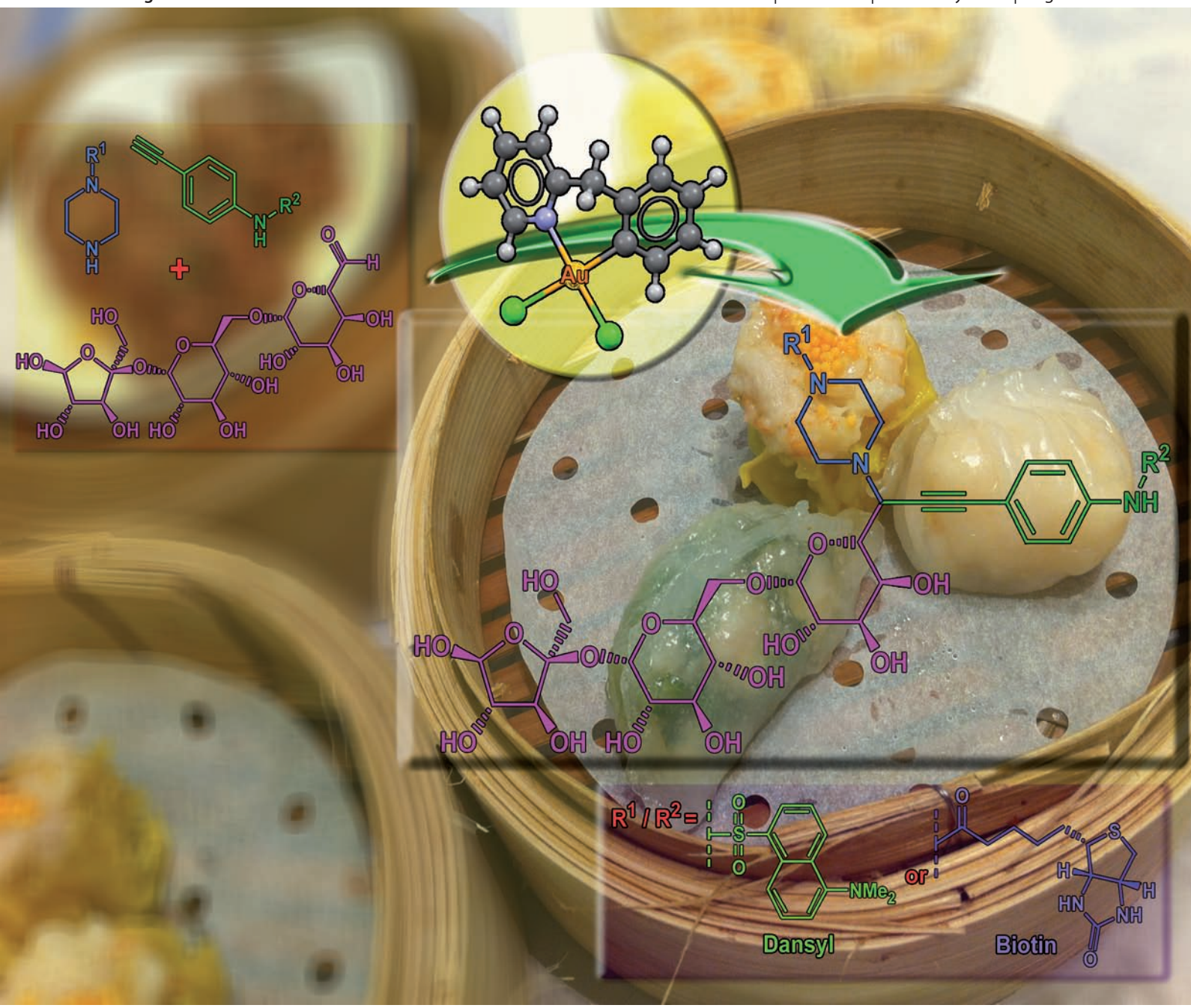

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COMMUNICATION

Gold-mediated bifunctional modification of oligosaccharides *via* a three-component coupling reaction†

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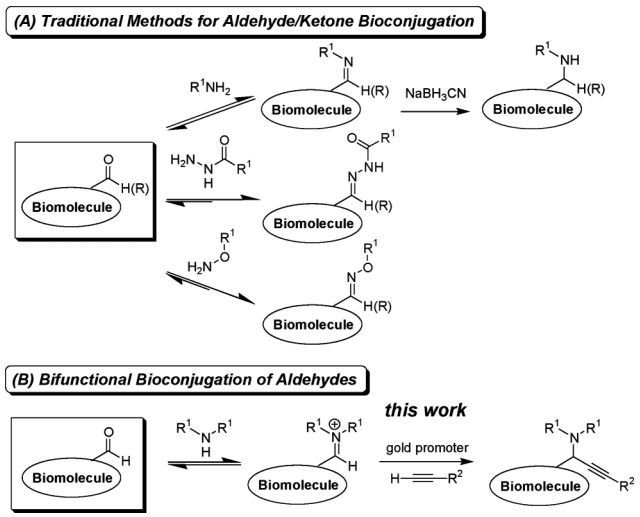
An efficient modular approach for single-site incorporation of two independent functionalities (amines and alkynes) into aldehyde-containing oligosaccharides concurrently by using a one-pot gold-mediated three-component coupling reaction in aqueous medium under mild conditions has been developed.

Selective modification of biomolecules is an essential tool in chemical biology, in which bioconjugation allows covalent attachment of probes and affinity tags to biomolecules for the study of complex biological systems.[1] However, selective modification of biomolecules is a challenging task due to the following reasons: (1) highly selective reagents should be used in bioconjugation as the functionalities of biomolecules cannot be protected; (2) the reactions have to be conducted under mild conditions, *i.e.* in aqueous medium within a narrow range of pH and temperature. Thus, there is a great interest in the development of new methods for selective modification of biomolecules.[2] Particularly, selective modification of oligosaccharides is of high importance because they play key roles in many biological processes, including cell signaling, host–pathogen interaction, and cancer cell metastasis.[3,4]

Aldehydes and ketones have long been used as bioorthogonal handles for modification of oligosaccharides, proteins and glycoproteins, as well as in glycomics and materials science.[5] Through periodate- or galactose oxidase-mediated alcohol oxidation and metabolic incorporation of ketone-containing amino acids/monosaccharides, aldehyde or ketone moieties are readily introduced to biomolecules.[1] The carbonyl groups can then be condensed with aliphatic/aromatic amines to generate imines and converted to stable amine derivatives by using $NaBH_3CN$ as a mild reducing agent (Scheme 1A). Under acidic conditions (pH 5–6), aldehydes/ketones couple with hydrazine and aminooxy compounds to give hydrazones and oximes, respectively. However,



Scheme 1 Aldehyde and ketone modification methods.

the slow reaction kinetics of the aldehyde/ketone modifications at neutral pH restricts their use in many biological applications. In addition, imines, hydrazones and oximes are susceptible to hydrolysis, and hence they have shortened lifetimes.[6] Recently, Dawson *et al.* developed anilines as excellent nucleophilic catalysts to accelerate the reaction rates of imine ligations under neutral reaction conditions.[7a–c] This method has been applied for *in vivo* cell surface labelling on sialylated glycoproteins and protein receptors.[7d–f] Although imine ligation can be catalyzed by anilines, the low hydrolytic stability of imines remains an intrinsic problem. Moreover, the aforementioned reactions can only allow incorporation of one functionality onto aldehydes/ketones at the same time.[8]

Gold catalysis has emerged as a frontier research area in organic synthesis, owing to its excellent chemoselectivity and reactivity, compatibility with aqueous reaction medium and mild reaction conditions.[9] Recently, we have developed gold-catalyzed synthesis of propargylamines *via* a three-component coupling reaction of aldehydes, amines and alkynes in water under mild reaction conditions.[10,11] As part of our program to develop site-selective modification of biomolecules,[12] we conceived that the gold-catalyzed three-component coupling reaction could be an appealing approach for aldehyde-based bifunctional bioconjugation

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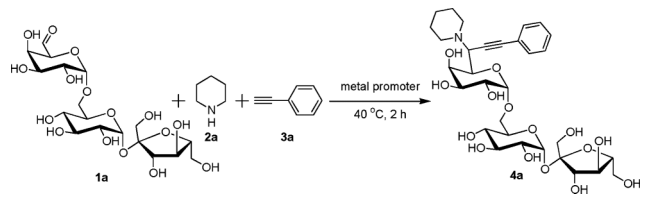
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob06429k

(Scheme 1B). Through the three-component coupling reaction, two different functionalities could be incorporated into aldehyde-containing biomolecules at a single site concurrently by using amine-/alkyne-linked biophysical probes/affinity tags in a one-pot reaction.

As a proof of concept, an initial study on the coupling reaction of unprotected D-raffinose aldehyde **1a** (10 mM), piperidine **2a** (10 equiv.), and phenylacetylene **3a** (10 equiv.) using [Au(C^N)Cl_2] (HC^N = 2-benzylpyridine) (1 equiv.) as a promoter in H_2O was performed at 40 °C for 2 h. We found that the bifunctionally modified D-raffinose **4a** with the hydroxyl groups remaining intact was obtained with 94% aldehyde conversion[13] by LC-MS analysis of the crude reaction mixture (Table 1, entry 1). No conversion of **1a** was found in the absence of [Au(C^N)Cl_2]. By varying the loading of [Au(C^N)Cl_2] to 0.5 and 2 equivalents, 88% and 93% aldehyde conversions were obtained, respectively (entries 2 and 3). Excellent conversion (94%) was also observed when the reaction was carried out at 25 °C (entry 4). This gold-mediated bioconjugation proceeded smoothly in PBS buffers (50 mM) of different pHs where similar conversions of 95% (at pH 5.1), 95% (at pH 6.2), 92% (at pH 7.1), and 98% (at pH 8.0) were obtained (entries 5–8). We also studied the compatibility of this reaction with common organic co-solvents. The reaction afforded 84% conversion of **1a** in H_2O/DMSO (1 : 1), while the conversions were found to be 42% and 54% for co-solvent systems H_2O/THF (1 : 1) and H_2O/*t*-BuOH (1 : 1) (entries 9–11). The activities of various metal promoters towards this bioconjugation reaction were examined. Using various Au(I) and Au(III) salts, up to 77% aldehyde conversion was found (entries 12–15). Moderate conversions (20–58%) of **1a** were found for CuBr, CuI, CuCl, and $CuBr_2$ catalysts (entries 16–19), while no conversion was observed for $AgNO_3$ (entry 20). In this regard, the gold cyclometallated complex [Au(C^N)Cl_2] was adopted for the subsequent studies.

Table 1 Screening conditions for bifunctional modification of D-raffinose aldehyde **1a** with different metal promoters and under various reaction conditions[a]



Entry	Promoter	Solvent	Aldehyde conv. (%)[b]
1	[Au(C^N)Cl_2]	H_2O	94
2	[Au(C^N)Cl_2]	H_2O	88[c]
3	[Au(C^N)Cl_2]	H_2O	93[d]
4	[Au(C^N)Cl_2]	H_2O	94[e]
5	[Au(C^N)Cl_2]	pH 5.1	95[f]
6	[Au(C^N)Cl_2]	pH 6.2	95[f]
7	[Au(C^N)Cl_2]	pH 7.1	92[f]
8	[Au(C^N)Cl_2]	pH 8.0	98[f]
9	[Au(C^N)Cl_2]	H_2O/DMSO (1 : 1)	84
10	[Au(C^N)Cl_2]	H_2O/THF (1 : 1)	42
11	[Au(C^N)Cl_2]	H_2O/*t*-BuOH (1 : 1)	54
12	$KAuCl_4$	H_2O	71
13	AuCl	H_2O	77
14	$AuCl_3$	H_2O	46
15	$AuBr_3$	H_2O	45
16	CuBr	H_2O	58
17	CuI	H_2O	39
18	CuCl	H_2O	33
19	$CuBr_2$	H_2O	20
20	$AgNO_3$	H_2O	0

[a] Unless otherwise specified, all reactions were carried out with D-raffinose aldehyde **1a** (10 mM), piperidine **2a** (10 equiv.), phenylacetylene **3a** (10 equiv.) and promoter (1 equiv.) in aqueous solvent at 40 °C for 2 h. [b] Determined by LC-MS. [c] [Au(C^N)Cl_2] (0.5 equiv.) [d] [Au(C^N)Cl_2] (2 equiv.) [e] Reaction performed at 25 °C. [f] PBS buffer (50 mM).

We studied the time course of the coupling reaction of D-raffinose aldehyde **1a**, piperidine **2a** and phenylacetylene **3a** in the presence of [Au(C^N)Cl_2] at 40 °C in H_2O (Fig. 1). When 10 equivalents of **2a** and **3a** were used, 45% aldehyde conversion was obtained in 30 min. Up to 90% conversion was observed in 1 h, and the conversion reached the maximum (94%) in 2 h. Using 5 equivalents of **2a** and **3a**, aldehyde conversion of 85% could be achieved in 4 h. No significant increase in conversion was found when 25 or 50 equivalents of **2a** and **3a** were used. We also carried out the time course experiments at 50 °C and the results were comparable to those performed at 40 °C (see the ESI†).

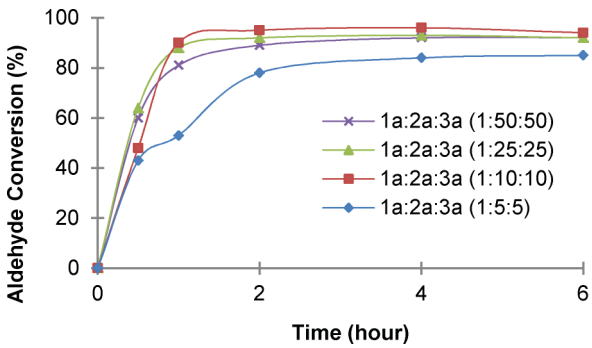


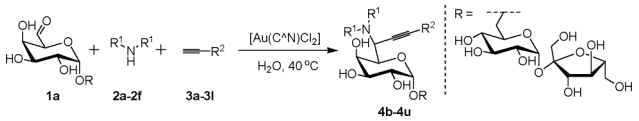
Fig. 1 Time course experiment of the gold-mediated bifunctional modification of D-raffinose aldehyde **1a** with piperidine **2a** and phenylacetylene **3a** at 40 °C.

Apart from D-raffinose aldehyde **1a**, the gold-mediated three-component coupling reaction also worked well for D-stachyose aldehyde **1b**, affording bifunctionally modified D-stachyose **5** with excellent conversion (99%) (see the ESI†). We performed the gold-mediated coupling reaction of unprotected methyl α-D-galactopyranoside aldehyde **1c** in milligram scale as a model reaction to provide support for the propargylamine formation[14] (see the ESI†).

In general, cross reactivity with ketone-containing metabolites such as pyruvate and oxaloacetate is problematic in the bioconjugation reaction of carbonyl compounds using aminooxy and hydrazine compounds in cell-based applications.[1,2a,2g] We found that no three-component coupling product was detected in the gold-catalyzed three-component coupling reactions of methyl pyruvate and oxaloacetic acid using **2a** and **3a** as the coupling partners, as indicated by ^{1}H NMR and ESI-MS analysis of the crude reaction mixture. These experiments reveal that the gold-catalyzed three-component coupling reaction is highly selective for aldehydes.[10b]

To examine the scope of this gold-mediated bifunctional modification, different combinations of amines and alkynes were employed. In the coupling with phenylacetylene **3a**, high conversion (98%) of D-raffinose aldehyde **1a** was observed when pyrrolidine **2b** was used (Table 2, entry 1). Coupling of prolinol derivatives

Table 2 The gold-mediated bifunctional modification of D-raffinose aldehyde **1a** with various amines and alkynes[a]



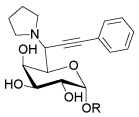
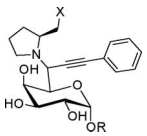
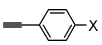
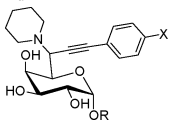
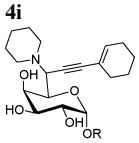
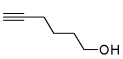
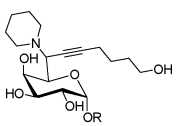
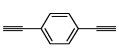
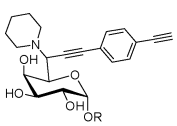
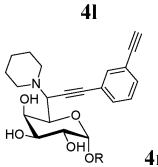
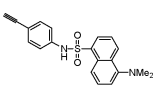
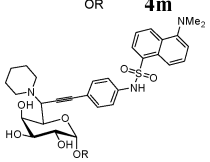
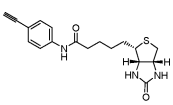
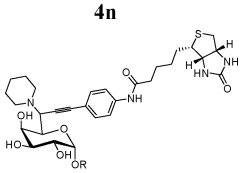
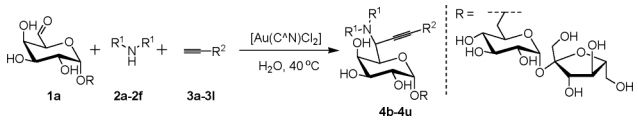
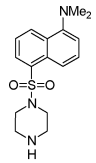
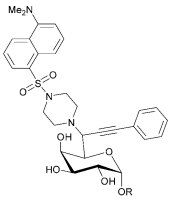
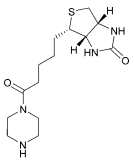
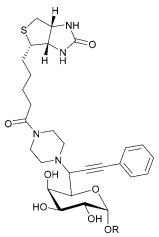
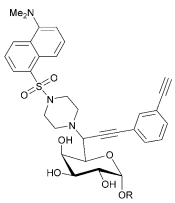
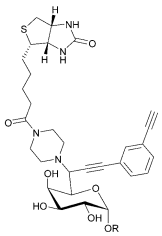
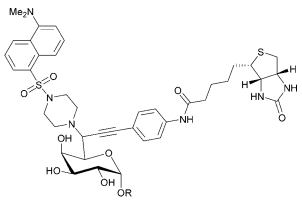
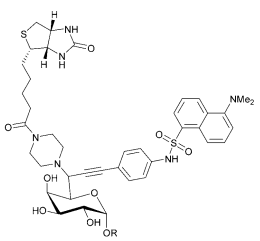
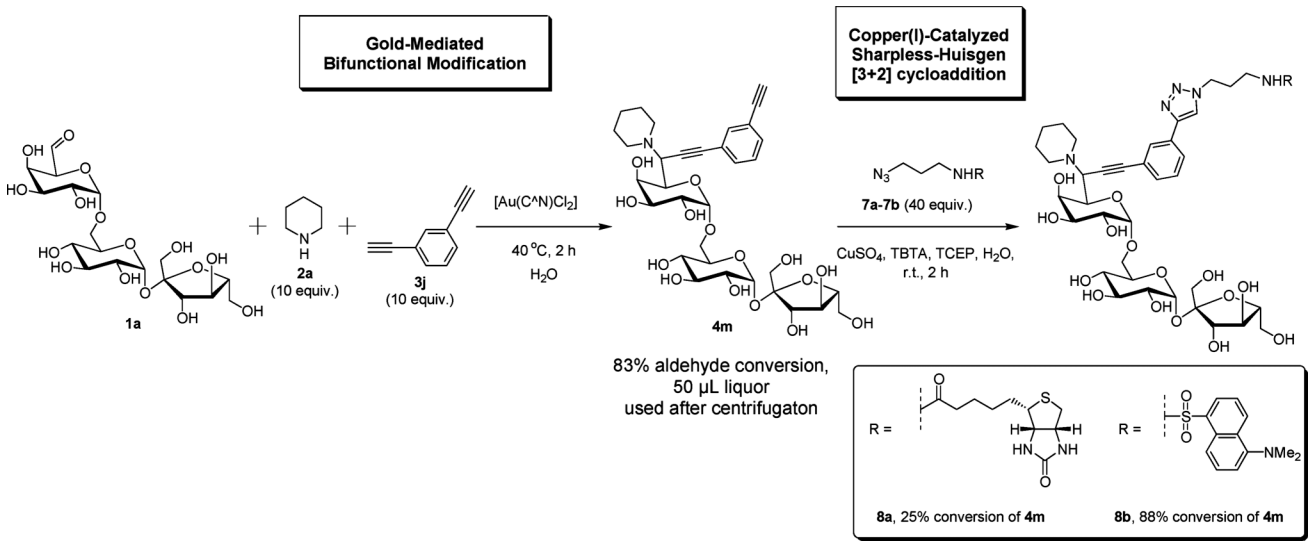
Entry	Amine	Alkyne	Product	Aldehyde Conv. (%)[b]
1	 **2b**	**3a**	 **4b**	98
				
2	X = OH, **2c**	**3a**	**4c**	81
3	X = OMe, **2d**	**3a**	**4d**	99
				
4	**2a**	X = OMe, **3b**	**4e**	97
5	**2a**	X = Cl, **3c**	**4f**	96
6	**2a**	X = Br, **3d**	**4g**	90
7	**2a**	X = NH_2, **3e**	**4h**	96
8	**2a**	X = CH_2OH, **3f**	**4i**	97
9	**2a**	 **3g**	 **4j**	70
10	**2a**	 **3h**	 **4k**	72
11	**2a**	 **3i**	 **4l**	84
12	**2a**	 **3j**	 **4m**	83
13	**2a**	 **3k**	 **4n**	92[c,d]
14	**2a**	 **3l**	 **4o**	47[c,d]

Table 2 (*Contd.*)



Entry	Amine	Alkyne	Product	Aldehyde Conv. (%)[b]
15	 **2e**	**3a**	 **4p**	88[c,e]
16	 **2f**	**3a**	 **4q**	70[c,e]
17	**2e**	**3j**	 **4r**	67[c,e]
18	**2f**	**3j**	 **4s**	88[c,e]
19	**2e**	**3l**	 **4t**	68[c,f]
20	**2f**	**3k**	 **4u**	65[c,g]

[a] Unless otherwise specified, all reactions were carried out with D-raffinose aldehyde **1a** (10 mM), amine (10 equiv.), alkyne (10 equiv.) and $[Au(C^N)Cl_2]$ (1 equiv.) in H_2O at 40 °C for 2 h. [b] Determined by LC-MS. [c] H_2O/DMSO (1 : 1) at 50 °C for 6 h. [d] Piperidine **2a** (50 equiv.) and alkyne **3k** or **3l** (1 equiv.) [e] Amine **2e** or **2f** (1 equiv.), alkyne **3a** or **3j** (50 equiv.) [f] Amine **2e** (1 equiv.), alkyne **3l** (5 equiv.) [g] Amine **2f** (1 equiv.), alkyne **3k** (1 equiv.).



Scheme 2 Bifunctional oligosaccharide derivative **4m** with a terminal alkyne moiety for sequential Cu(I)-catalyzed [3 + 2] cycloaddition with azides **7a–7b**.

bearing free –OH (**2c**) and –OMe groups (**2d**) afforded products **4c** and **4d** in 81% and 99% conversions, respectively (entries 2 and 3).

The coupling reactions of arylacetylenes bearing various *p*-substituents with **1a** and **2a** were studied. High conversion (97%) was observed for 4-ethynylanisole **3b** having an electron-donating *p*-OMe substituent (entry 4). For arylacetylenes containing electron-withdrawing *p*-Cl (**3c**) and *p*-Br (**3d**) substituents, conversions of 96% and 90% were obtained, respectively (entries 5 and 6). Arylacetylenes with free *p*-NH_2 (**3e**) and *p*-CH_2OH (**3f**) groups gave the corresponding products in 96% and 97% conversions (entries 7 and 8). Coupling of 1-ethynylcyclohexene **3g** led to **4j** in 70% conversion while aliphatic alkyne bearing a free –OH group (**3h**) afforded **4k** in 72% conversion (entries 9 and 10).

The bioconjugation that involves covalent attachment of biophysical probes to biomolecules allows the generation of functionalized bioconjugates for biological studies. The commonly used biophysical probes in bioconjugation include: (1) terminal alkyne handles for bioorthogonal coupling with organic azides *via* click chemistry, (2) fluorescent probes for chromatographic analysis and molecular imaging, and (3) biotin tags for streptavidin-based immobilization.

On the basis of the above studies, we employed this gold-mediated three-component coupling reaction to incorporate terminal alkyne handles, fluorescent probes, and biotin tags to D-raffinose aldehyde **1a**. We found that coupling of bifunctional linkers, such as 1,4-diethynylbenzene **3i** and 1,3-diethynylbenzene **3j**, gave terminal alkyne-modified D-raffinoses **4l** (84%) and **4m** (83%), respectively (entries 11 and 12). Coupling of dansyl-linked alkyne **3k** and biotin-linked alkyne **3l** with **2a** proceeded smoothly to give corresponding products **4n** (92%) and **4o** (47%) (entries 13 and 14). Alternatively, using dansyl-linked amine **2e** and biotin-linked amine **2f** with **3a**, products **4p** (88%) and **4q** (70%) could be obtained (entries 15 and 16). The modular versatility in this gold-mediated three-component coupling reaction could be exemplified by construction of bifunctionally modified D-raffinoses with diverse combinations of terminal alkyne–dansyl (**4r**), terminal alkyne–biotin (**4s**), and dansyl–biotin (**4t** and **4u**) functionalities with good aldehyde conversions (65–88%) (entries 17–20). It should be pointed out that only 1 equivalent of each amine **2f** and alkyne **3k** was required for the synthesis of **4u** with 65% conversion (entry 20).

Note that the gold-mediated bifunctional modification/copper(I)-catalyzed [3 + 2] cycloaddition reaction sequence provides a convenient access to a diversity of multifunctional oligosaccharides (Scheme 2). With the introduction of a terminal alkyne moiety on oligosaccharide derivatives *via* gold-mediated bifunctional modification, further bioorthogonal transformation is possible. We have subjected the gold-mediated bifunctionally modified product **4m** (Table 2, entry 12) to subsequent copper(I)-catalyzed [3 + 2] cycloaddition.[15] A clear liquor of **4m** after centrifugation was pipetted and then treated with biotin- (**7a**) and dansyl-linked azides (**7b**) in aqueous medium for 2 h, affording triazole products **8a** and **8b** with 25% and 88% conversions of **4m**, respectively, as indicated by LC-MS analysis. Therefore, it is interesting to note that the gold-mediated reaction could be extended for further modification after introduction of two different functionalities. This gold-mediated coupling reaction is suitable for subsequent synthetic elaboration without tedious clean-up and purification procedures.

The present gold-mediated three-component coupling reaction allows single-site incorporation of two different functionalities (amines and alkynes) onto biomolecules in a one-pot reaction. Since multi-component coupling reactions[16] have greatly facilitated organic synthesis and drug discovery processes in both academia and industry by combinatorial synthesis of diverse molecular structures, it is envisioned that this gold-mediated three-component coupling reaction will open up a new direction in bioconjugation to expand the scope of bioconjugates of high structural diversity in a cost- and time-efficient manner.

The solubility of biophysical probes/affinity tags in water remains a concern in bioconjugation. In general, functionalized alkynes have lower solubility in water. As a three-component coupling reaction, the present approach allows the installation

of water-insoluble functionalities *via* an amine component that is of higher water solubility.

In summary, a new modular approach for single-site incorporation of two independent functionalities (amines and alkynes) into aldehyde-containing oligosaccharides by using a one-pot gold-mediated three-component coupling reaction has been developed. This gold-mediated bifunctional modification reaction proceeded smoothly in excellent conversion (up to 99%) with high functional group tolerance in aqueous medium under mild reaction conditions.

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