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Modular synthesis of propargylamine modified cyclodextrins by a gold(III)-catalyzed three-component coupling reaction†

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An efficient modular approach for the synthesis of propargylamine modified β-cyclodextrins has been developed. Using mono-(6-benzylamino-6-deoxy)-β-cyclodextrins, formaldehyde, and alkynes, mono-(6-(benzylpropargyl)amino-6-deoxy)-β-cyclodextrins have been synthesized through a three-component coupling reaction catalyzed by gold(III) salt in water at 40 °C.

Cyclodextrins (CDs) are naturally occurring cyclic oligosaccharides consisting of α-1,4-D-glucopyranose units. The commonly used cyclodextrins with six, seven, and eight glucopyranose units are referred to as α-, β-, and γ-cyclodextrins, respectively (Fig. 1a). Cyclodextrin is an amphipathic molecule bearing a hydrophilic exterior surface and a hydrophobic interior cavity (Fig. 1b). Owing to the hydrophilic surface, cyclodextrins are water-soluble. The hydrophobic cavity of cyclodextrins allows "host–guest" inclusion complex formation with a wide variety of guest molecules through hydrophobic interaction. Therefore, the use of cyclodextrins and their modified derivatives as versatile supramolecular hosts has been widely employed in supramolecular catalysis, enzymatic mimics, analytical chemistry, and the pharmaceutical and food industry.[1–9]

In general, modified cyclodextrins exhibit distinctive properties compared with native cyclodextrins. Modification of cyclodextrins provides novel derivatives with unique structures and functions to support the development of different research fields.[1,4–9] In the past decades, various methods for cyclodextrin modification have been developed to fine-tune their physicochemical properties (solubility, inclusion complexation properties, *etc.*). In particularly, 6-OTs monosubstituted cyclodextrins have been employed as orthogonal handle for conjugation with different functional molecules (Scheme 1a).[10–12] Through transformation of the OTs group of the mono[6-*O*-(*p*-toluenesulfonyl)]-cyclodextrin (6-OTs-CD), amine and alkyne functionalities could be easily introduced into cyclodextrins. Further synthetic elaborations through amidation and click reaction with carboxylic acids/halides and azides containing molecules offer an easy access to multifunctional molecules. Moreover, alkyne containing cyclodextrins function as versatile building blocks for the synthesis of multifunctional cyclodextrins through click reaction, 1,3-dipolar cycloaddition, and Sonogashira cross-coupling

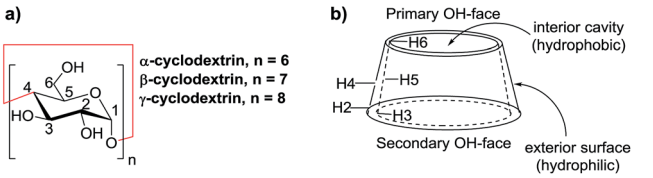
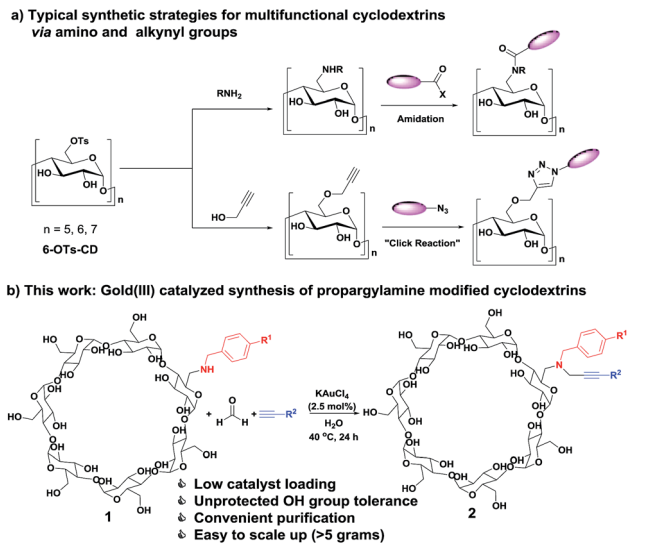


Fig. 1 Chemical structures of cyclodextrins.



Scheme 1 (a) Typical synthetic strategies for multifunctional cyclodextrins *via* amino and alkynyl groups; (b) gold(III) catalyzed synthesis of propargylamine modified cyclodextrins.

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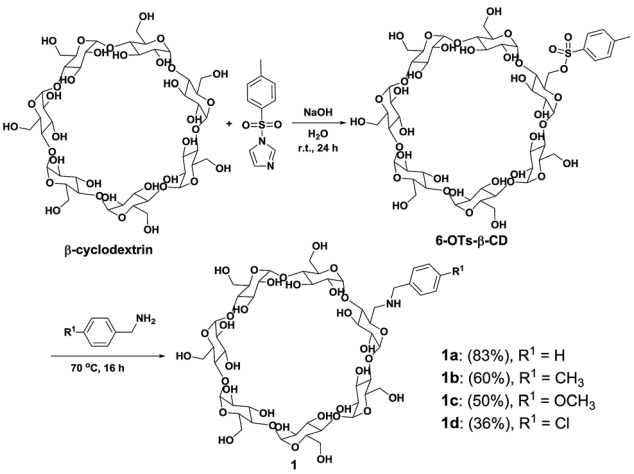
reaction.[13,14] However, cyclodextrin modification is still a challenging task in synthetic chemistry due to the multiple hydroxyl groups present at the 2-, 3-, and 6-positions competing with reactants, leading to complex product formation and difficult product purification. Thus, there remains a significant interest to develop new approaches for the synthesis of multifunctional cyclodextrins.

Over the years, we have been developing gold catalysis for organic synthesis,[15–18] and bioconjugation of oligosaccharides, peptides and proteins.[19–21] Efficient methods for the synthesis of multifunctional biomolecules *via* Morita–Baylis–Hillman reaction and gold catalyzed/mediated reactions have also been developed in our group.[19–22] Particularly, a 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.[17,19] As cyclodextrins are cyclic oligosaccharides, it is envisaged that multifunctional propargylamine modified cyclodextrins could be synthesized from a gold-catalyzed three component coupling reaction[23–25] of amine containing cyclodextrins, aldehydes, and alkynes.

Here we first present an efficient method for the synthesis of a new class of propargylamine modified β-cyclodextrins through a modular approach of gold(III)-catalyzed three component coupling reaction of amine containing cyclodextrins, formaldehyde, and alkynes in water at 40 °C (Scheme 1b). Using mono-(6-benzylamino-6-deoxy)-β-cyclodextrins (**1**, 6-BA-β-CD), formaldehyde, and various alkynes, mono-(6-(benzylpropargyl)amino-6-deoxy)-β-cyclodextrins (**2**, 6-BPA-β-CD) have been achieved in moderate to good yields with excellent purity through convenient precipitation in acetone and recrystallization in water successively. Notably, the reaction proceeded with high chemoselectivity for formaldehyde and remarkable functional group compatibility for the unprotected hydroxyl groups of mono-(6-benzylamino-6-deoxy)-β-cyclodextrins **1**.

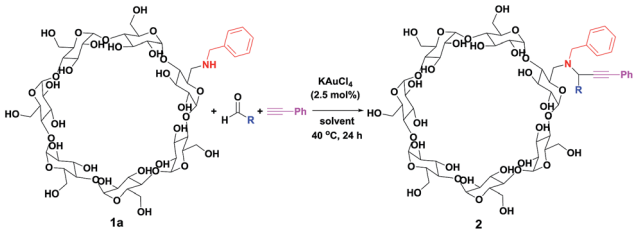
One key challenge for selective modification of cyclodextrins is the competitive reactions of the hydroxyl groups at the 2-, 3- and 6-positions. Highly reactive reagents tend to non-selectively react with the hydroxyl groups of any positions, while less reactive reagents allow selective modification of the hydroxyl groups at the 6-position.[1] Typically, mono-, and multi-(6-tosyl) cyclodextrins are the most commonly used precursors for the synthesis of a wide variety of 6-position modified cyclodextrins. Therefore, we set out to synthesize mono-(6-benzylamino-6-deoxy)-β-cyclodextrins (**1**, 6-BA-β-CD)[26] from 6-OTs-β-CD as the amine component for the gold(III)-catalyzed three component coupling reaction. In this regard, 6-OTs-β-CD was synthesized *via* the reaction of β-cyclodextrin and *p*-toluenesulfonyl imidazole in alkaline aqueous solution according to literature procedure (Scheme 2).[27] Starting from 6-OTs-β-CD, 6-BA-β-CD **1** was synthesized accordingly.[28] Upon treatment with benzylamine as solvent and reactant at 70 °C for 16 h, 6-OTs-β-CD was converted to 6-BA-β-CD **1a** with 83% yield. Then, various substituted benzylamines were used to synthesize 6-BA-β-CDs (**1b–1d**) under the same reaction conditions with moderate to good yields (36–83%, Scheme 2).



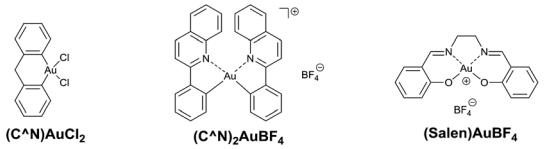
Scheme 2 Synthetic route of mono-(6-benzylamino-6-deoxy)-β-cyclodextrins **1**.

6-BA-β-CD (**1a**) was used as the amine component coupling with phenylacetylene and various aldehydes, as well as different solvents and transition-metal catalysts were used to study the reaction conditions (Table 1). Using **1a** (0.1 mmol), benzaldehyde (1.0 mmol), and phenylacetylene (1.0 mmol) with $KAuCl_4$ (2.5 mol%) as catalyst in water at 40 °C for 24 h gave no desired three component coupling product (Entry 1). Benzaldehydes bearing electron-donating group (4-OMe) and electron-deficient group (4-NO_2) on the phenyl ring also did not afford the desired product (Entries 2 and 3). To our delight, when formaldehyde was used as the aldehyde component under the same reaction conditions, the expected product **2a** was isolated in 50% yield (Entry 4). Yet, only a trace amount or no product was obtained when ACN, THF and toluene were used instead of H_2O as solvent (Entries 5–7). $AuCl_3$ and AuCl gave comparable yield in 46% and 41%, respectively (Entries 8 and 9). A trace amount of product was obtained by using $HAuCl_4$ as the catalyst (Entry 10). Other gold(III) complexes $[(C\hat{}N)AuCl_2]$ and $[(C\hat{}N)_2AuBF_4]$ ($HC\hat{}N$ = 2-phenylpyridine or 2-phenylquinoline) were also employed as the catalyst for the reaction, but only a trace amount of coupling product was detected by ESI-MS analysis (Entries 11 and 12). Note that 34% yield of product was obtained when Salen-gold(III) complex $[(Salen)AuBF_4]$ was used as catalyst (Entry 13). Then, the catalytic effect of various transition-metal catalysts, including $Cu(OAc)_2$, $Cu(OTf)_2$, AgOTf, $NiBr_2$, $Zn(OAc)_2$ and $RuCl_3$, for this reaction was examined (Entries 14–19). The results showed that only $RuCl_3$ catalyzed this reaction to give product in 25% yield. Furthermore, aliphatic aldehydes, such as acetaldehyde, butyraldehyde and heptaldehyde, did not give the corresponding products with combination of amine **1a** and phenylacetylene (Entries 20–22). These results indicated that this three component coupling reaction proceeded with high chemoselectivity for formaldehyde and the use of simple gold salt $KAuCl_4$ as the catalyst and water as the solvent are essential. Moreover, a primary amine modified cyclodextrin **1aa** was synthesized and employed as amine component coupling with phenylacetylene and various aromatic and aliphatic aldehydes.

Table 1 Screening conditions of three component coupling reaction[a]



Entry	R	Catalyst	Solvent	Yield of 2[b] (%)
1	Ph	$KAuCl_4$	H_2O	0
2	4-$OMeC_6H_4$	$KAuCl_4$	H_2O	0
3	4-$NO_2C_6H_4$	$KAuCl_4$	H_2O	0
4	H	$KAuCl_4$	H_2O	50
5	H	$KAuCl_4$	ACN	Trace[c]
6	H	$KAuCl_4$	THF	Trace[c]
7	H	$KAuCl_4$	Toluene	0
8	H	$AuCl_3$	H_2O	46
9	H	AuCl	H_2O	41
10	H	$HAuCl_4$	H_2O	Trace[c]
11	H	$(C^N)AuCl_2$	H_2O	Trace[c]
12	H	$(C^N)_2AuBF_4$	H_2O	Trace[c]
13	H	$(Salen)AuBF_4$	H_2O	34
14	H	$Cu(OAc)_2$	H_2O	0
15	H	$Cu(OTf)_2$	H_2O	0
16	H	AgOTf	H_2O	0
17	H	$NiBr_2$	H_2O	0
18	H	$Zn(OAc)_2$	H_2O	0
19	H	$RuCl_3$	H_2O	25
20	CH_3	$KAuCl_4$	H_2O	0
21	n-C_3H_7	$KAuCl_4$	H_2O	0
22	n-C_6H_{13}	$KAuCl_4$	H_2O	0

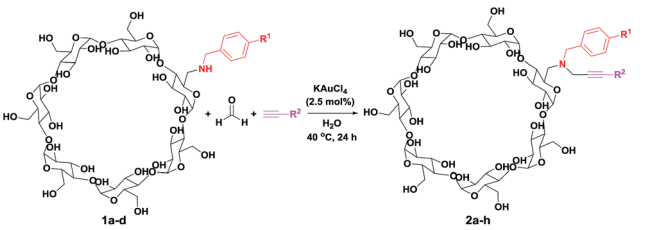


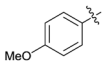
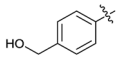
[a] Reaction conditions: **1a** (0.1 mmol), aldehyde (1.0 mmol), phenylacetylene (1.0 mmol), 40 °C, 24 h. [b] Isolated yield. [c] Detected by ESI-MS analysis.

Yet, for all of tested aldehydes, no desired three component coupling products were obtained (see ESI, Table S1†).

To examine the substrate scope of this three component coupling reaction, we extended our studies to various combinations of 6-BA-β-CD **1** and alkynes. As depicted in Table 2, this synthetic strategy works well for a wide range of substrates with moderate to good yields (up to 67%). Coupling of **1a** with formaldehyde and phenylacetylene led to propargylamine modified β-cyclodextrin **2a** in 50% yield (Entry 1). Coupling product **2a** was characterized by NMR spectroscopic techniques (including ^1H, ^{13}C, COSY, ROESY, HMQC and HMBC experiments) and ESI-MS spectrometry. Using mono-(6-benzylamino-6-deoxy)-β-cyclodextrins **1b–1d** with electron-donating group (Me, OMe) and electron-deficient group (Cl) on the phenyl ring of the benzyl moieties also proceeded smoothly, and the corresponding coupling products **2b–2d** were obtained in good

Table 2 Screening of substrate scope of propargylamine modified β-cyclodextrins and alkynes[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	H		**2a**	50[c]
2	CH_3		**2b**	51
3	OCH_3		**2c**	42
4	Cl		**2d**	49
5	H		**2e**	50
6	H		**2f**	67
7	H		**2g**	52
8	H		**2h**	26

[a] The reaction was conducted with β-CD amine **1** (0.8 mmol), formaldehyde (8.0 mmol), alkyne (8.0 mmol), $KAuCl_4$ (2.5 mol%) in water (10 mL) at 40 °C for 24 h. [b] Isolated yield. [c] β-CD amine **1** (0.1 mmol), formaldehyde (1.0 mmol), alkyne (1.0 mmol).

yields (42–51%, Entries 2–4). Using **1a**, various aromatic and aliphatic alkynes also reacted with formaldehyde to give **2e–2h** in 26–67% yield (Entries 5–8). Notably, the reactive functional groups (hydroxyl, cyclohexenyl) on the alkynes remain intact after the coupling reactions (**2f** and **2h**, Entry 6 and Entry 8).

In conclusion, a new method for convenient preparation of propargylamine modified β-cyclodextrins has been established through a gold(III)-catalyzed three component coupling reaction. This modular synthetic strategy would be extended to conversion of cyclodextrins bearing secondary amine moieties to propargylamine modified cyclodextrin derivatives. Given the synthetic utility of propargylamines, it is envisioned that these propargylamine modified β-cyclodextrins could serve as versatile synthetic building blocks for the development of new cyclodextrin derivatives as hosts for applications on supramolecular catalysis and drug delivery.

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