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An Expeditious Synthesis of Sialic Acid Derivatives by Copper(I)-Catalyzed Stereodivergent Propargylation of Unprotected Aldoses

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S Supporting Information
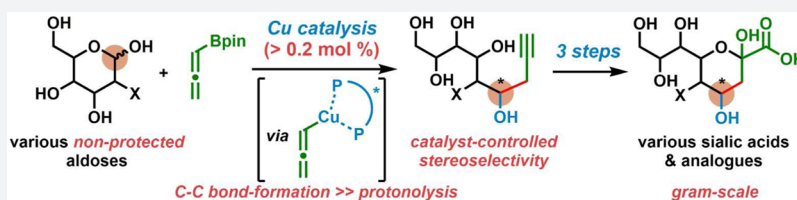
ABSTRACT: We developed a copper(I)-catalyzed stereodivergent anomeric propargylation of unprotected aldoses as a facile synthetic pathway to a broad variety of sialic acid derivatives. The soft allenylcopper(I) species, catalytically generated from stable allenylboronic acid pinacolate (2), is unusually inert to protonolysis by the multiple hydroxy groups of the substrates and thereby functions as a carbon nucleophile. The key additive $B(OMe)_3$ facilitated ring-opening of the nonelectrophilic cyclic hemiacetal forms of aldoses to the reactive aldehyde forms. The chirality of the catalyst, and not the internal stereogenic centers of substrates, predominantly controlled the stereochemistry of the propargylation step; i.e., the diastereoselectivity was switched simply by changing the catalyst chirality. This is the first nonenzyme catalyst-controlled stereodivergent C–C bond elongation at the anomeric center of unprotected aldoses, which contain multiple protic functional groups and stereogenic centers. The propargylation products can be expeditiously transformed into naturally occurring and synthetic sialic acid derivatives in a simple three-step sequence. This synthetic method, which requires no protecting groups, can be performed on a gram-scale and thus offers general and practical access to various sialic acid derivatives from unprotected aldoses.

INTRODUCTION

Minimizing the use of protecting groups is critically important[1] toward realizing efficient molecular syntheses with high atom-[2] and step-economy.[3] As a synthetic method with reduced use of protecting groups, the development of catalytic chemoselective and stereocontrolled nucleophilic alkylation of carbonyl substrates containing unprotected protic functional groups is a formidable challenge. Because it is generally difficult to separate the nucleophilicity and Brønsted basicity of polar organometallic alkylating reagents, protonolysis of the reactive species by protic functional groups can be competitive to the desired C–C bond-formation.[4] The ruthenium- and iridium-catalyzed asymmetric allylation and propargylation developed by Krische[5] and the copper-catalyzed heterocupration of allenes followed by asymmetric addition developed by us are notable exceptions.[6] On the basis of our efforts to further minimize the use of protecting groups in complex molecule synthesis, we here report the first catalyst-controlled stereodivergent anomeric propargylation of unprotected aldoses, hidden aldehydes[7] containing multiple protic functional groups and stereogenic centers.[8] We applied the method to an expeditious and practical protecting-group-free synthesis of various stereo-isomeric sialic acid derivatives.

Sialic acids, which comprise a polyfunctionalized 9-carbon α-keto carboxylic acid skeleton, are present at the nonreducing end of glycan chains of various glycoproteins and glycolipids.

N-Acetylneuraminic acid (Neu5Ac), N-glycolylneuraminic acid (Neu5Gc), and 2-keto-3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN) are representative examples of the more than 50 naturally occurring sialic acids (Figure 1a).[9] Because of their
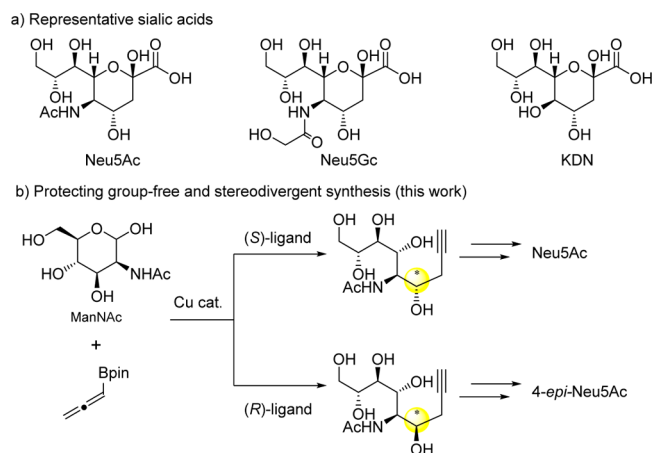

Figure 1. (a) Representative sialic acids and (b) protecting group-free and stereodivergent synthesis of sialic acid derivatives (this work).
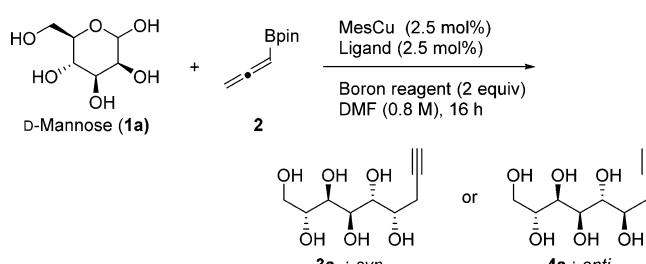
remarkable structural diversity and prevalent distribution on the outer surfaces of cells, many extracellular proteins such as siglecs,[10] selectins,[11] and sialidases[12] use sialic acids as specific recognition markers. The sialic acid−protein interactions are of special interest in sialobiology and drug discovery, since they regulate a variety of fundamental biologic events, including cell−cell recognition,[13] neurobiologic functions,[14] cancer metastasis,[15] and viral infections.[16] In the quest for selective inhibitors of these interactions,[17] synthetic methods enabling a facile access to a wide variety of sialic acid derivatives are pivotal. Sialic acid derivatives containing unnatural stereochemistry are potential inhibitors of sialic acid-recognizing proteins.[18] In this context, several elegant sialic acid syntheses from readily available carbohydrates have been developed, including protecting-group-free chemical syntheses[19] and enzymatic syntheses.[20] A practical method flexibly applicable to the synthesis of various stereoisomers of sialic acid derivatives, however, has not yet been reported. The carbon skeleton elongation process, both in chemical and enzymatic methods, has always been governed by the internal stereochemistry of the substrates,[21] obstructing access to unnatural stereoisomers.

To overcome the limitation, we envisaged the use of an asymmetric copper catalyst, capable of controlling the stereochemistry of the C−C bond-formation at the anomeric carbon of unprotected aldoses. We recently reported a copper(I)-catalyzed anomeric aminoalkynylation of unprotected aldoses.[22] In this reaction, the C−C bond-formation is able to proceed in the presence of multiple unprotected hydroxy groups, due to a unique characteristic of the soft organocopper(I) species,[23] which is generated catalytically in situ; namely, the Brønsted basicity is attenuated relative to the nucleophilicity.[6,24] However, this reaction is limited by the fact that the stereoselectivity is substrate-dependent and not controlled by the catalyst. The results of this study prompted us to speculate that a reaction, proceeding through a cyclic six-membered transition state, should render catalyst-controlled stereochemistry more feasible.[25] On the basis of this hypothesis, we investigated a copper-catalyzed anomeric propargylation of unprotected aldoses, wherein the aldehyde forms of the aldoses act, in contrast to the iminium ions in the case of the aminoalkynylation, as the electrophiles.
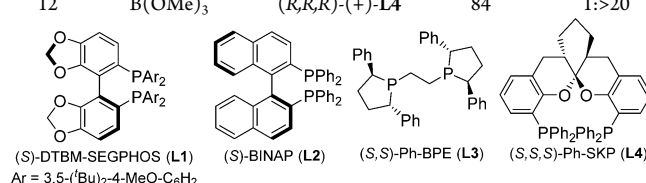
■ RESULTS AND DISCUSSION

We began our investigations using D-mannose (**1a**) and allenylboronate (**2**; 1.6 equiv) as substrates (Table 1). The active copper alkoxide catalyst was generated in situ from the reaction of mesitylcopper (MesCu), **1a**, and the corresponding ligand. Initial screening of several fundamental parameters, such as ligand, solvent, temperature, and reaction time, provided only trace amounts of the products **3a** and **4a** (Table 1; entries 1 and 2). The observed low reactivity should most likely be attributed to the low concentration of the reactive aldehyde form of **1a**.[7] In order to increase the concentration of this aldehyde, we found that the use of a proper hemiacetal ring-opening additive was essential. While the addition of boric acid[22] did not improve the reactivity (entry 3), addition of B(OMe)₃ promoted the desired reaction, affording **3a** and **4a** in a combined yield of 17% (3:1 diastereoisomer ratio) in the presence of 2.5 mol % of an achiral Cu-Xantphos catalyst (entry 4). Although the use of chiral ligands, such as DTBM-SEGPHOS (**L1**; entries 5 and 6), BINAP (**L2**; entries 7 and 8), and Ph-BPE (**L3**; entries 9 and 10), did not induce significant

Table 1. Optimization of the Stereodivergent Propargylation of D-Mannose[a]

entry	boron reagent	ligand	yield (%)	3a:4a
1	none	none	0	
2	none	xantphos	trace	
3	B(OH)₃	xantphos	trace	
4	B(OMe)₃	xantphos	17	3:1
5	B(OMe)₃	(S)-L1	8	1:1
6	B(OMe)₃	(R)-L1	7	1:1
7	B(OMe)₃	(S)-L2	36	1:1
8	B(OMe)₃	(R)-L2	38	1:1
9	B(OMe)₃	(S,S)-L3	43	4:1
10	B(OMe)₃	(R,R)-L3	50	1:1
11	B(OMe)₃	(S,S,S)-(−)-L4	95	>20:1
12	B(OMe)₃	(R,R,R)-(+)-L4	84	1:>20

(S)-DTBM-SEGPHOS (**L1**)   (S)-BINAP (**L2**)   (S,S)-Ph-BPE (**L3**)   (S,S,S)-Ph-SKP (**L4**)
Ar = 3,5-(ᵗBu)₂-4-MeO-C₆H₂

[a]General reaction conditions: **1a** (0.1 mmol), **2** (0.16 mmol), MesCu (2.5 mol %), ligand (2.5 mol %), DMF (125 μL), room temperature, 16 h. Yield and diastereoisomer ratio were determined by ¹H NMR analysis, using DMPU as an internal standard.

diastereoselectivity, Ph-SKP (**L4**)[26] turned out to be exceptional. The use of (S,S,S)-**L4** (entry 11) furnished the *si*-face adduct **3a** in high yield and excellent diastereoselectivity, while using (R,R,R)-**L4** (entry 12) predominantly afforded the *re*-face adduct **4a**. Thus, both diastereomers, **3a** and **4a**, were accessible selectively in high yield and stereodivergency, simply by switching the absolute configuration of the chiral copper catalyst.

A proposed catalytic cycle for this process is shown in Figure 2. Initially, copper alkoxide **A** should be generated from the deprotonation of an aldose hydroxy group by MesCu. Subsequently, **A** should undergo transmetalation with the allenylboronate **2** to produce allenylcopper **B** as the active species. The concentration of the reactive aldehyde **C**, in equilibrium with the cyclic hemiacetal form of the aldose, would be increased by the addition of B(OMe)₃.[27] This should favor the stabilization of the aldehyde form through the formation of reversible covalent bonds between the hydroxy groups of the aldose. Thus, the C−C bond-forming reaction would proceed via a six-membered transition state, **D**, to afford copper alkoxide **E**. Finally, transmetalation between **E** and **2** would regenerate allenylcopper species **B**. Subsequent cleavage of the O−B bond in **F** during the workup would provide the desired product **3**.

Having established optimal conditions for this highly diastereoselective propargylation (condition A), we next examined the substrate scope (Table 2). Using ligands with
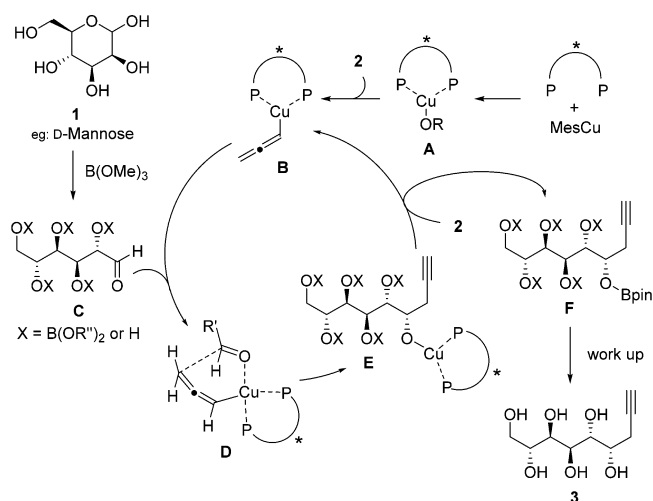
Figure 2. Proposed catalytic cycle for the catalyst-controlled stereodivergent propargylation of unprotected aldoses.

either (*S*,*S*,*S*)- or (*R*,*R*,*R*)-configuration, the reaction proceeded in high yield and excellent diastereoselectivity with a variety of

aldoses, including five- and six-carbon aldoses (entries 1−12). Relative to other aldoses, glucose (**1c**) was less reactive, presumably due to the formation of a stable cyclic hemiacetal, wherein all the substituents on the tetrahydropyran ring occupy equatorial positions. The concentration of the reactive aldehyde thus remains very low, even in the presence of B(OMe)$_3$. Nevertheless, increasing the amount of **2** to 5 equiv and the reaction temperature to 60 °C furnished **3c** and **4c** in good yield, albeit with moderate diastereoselectivity for **4c** (entries 5 and 6). We also found that condition A was not suitable for 2-deoxy-aldoses, probably due to a faster protonolysis of allenylcopper **B** relative to the desired C−C bond-formation. As a consequence, we decided to re-examine milder reaction conditions, with the aim of decreasing the concentration of the in situ-generated allenylcopper species (Figure 2). During this examination, we observed that the combination of Cu-ClO$_4$(MeCN)$_4$ and CF$_3$COOK generates the milder Lewis base CF$_3$COOCu, which proved effective for the propargylation of 2-deoxy-aldoses (condition B).[27] Upon applying condition B, both five- and six-carbon 2-deoxy-aldoses afforded the corresponding products in good yield (entries 13−18). Among the 2-acetoamido aldoses (entries 19−24), condition

Table 2. Substrate Scope of the Stereodivergent Propargylation of Unprotected Aldoses

Entry	Substrate	Cond.[a]	x	Product	Yield (%),[b] dr[c] with (S,S,S)-L4 or (R,R,R)-L4	Entry	Substrate	Cond.	x	Product	Yield (%),[b] dr[c] with (S,S,S)-L4 or (R,R,R)-L4
1	D-Mannose (1a)	A	1.6		3a: 90%, >20:1	13	2-Deoxy-D-Ribose (1g)	B	3		3g: 65%, 18:1
2					4a: 81%, 1:>20	14					4g: 53%, 1:>20
3[d,e]	D-Galactose (1b)	A	3		3b: 73%, 11:1	15	2-Deoxy-D-Galactose (1h)	B	3		3h: 74%, >20:1
4[d,e]					4b: 66%, 1:9.2	16					4h: 67%, 1:10
5[d,f,g]	D-Glucose (1c)	A	5		3c: 76%, >20:1	17	2-Deoxy-D-Glucose (1i)	B	3		3i: 59%, >20:1
6[d,f,g]					4c: 72%, 1:3.5	18					4i: 52%, 1:17
7	D-Lyxose (1d)	A	1.6		3d: 84%, >20:1	19[d]	N-Acetyl-D-Mannosamine (1j)	A	3		3j: 70%, >20:1
8					4d: 81%, 1:>20	20[d]					4j: 51%, 1:>20
9	D-Arabinose (1e)	A	1.6		3e: 95%, >20:1	21[e,h]	N-Acetyl-D-Galactosamine (1k)	B	5		3k: 55%, >20:1
10					4e: 93%, 1:>20	22[e,h]					4k: 40%, 1:>20
11[d,e]	D-Xylose (1f)	A	1.6		3f: 65%, >20:1	23[e,h]	N-Acetyl-D-Glucosamine (1l)	B	5		3l: 45%, 15:1
12[d,e]					4f: 60%, 1:>20	24[e,h]					4l: 51%, 1:>20

[a]Condition A: MesCu (2.5 mol %), **L4** (2.5 mol %), B(OMe)$_3$ (2 equiv), DMF, room temperature; Condition B: CuClO$_4$(MeCN)$_4$ (2.5 mol %), **L4** (2.5 mol %), CF$_3$COOK (5 mol %), molecular sieves (MS 3A), B(OMe)$_3$ (2 equiv), DMF, room temperature. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis of the crude mixture. [d]MS 3A was added. [e]The reaction was carried out at 40 °C. [f]The reaction was carried out at 60 °C. [g]B(OMe)$_3$ (6 equiv) was added. [h]3.8 mol % of CuClO$_4$(MeCN)$_4$ and 2.5 mol % of **L4** were used; B(OMe)$_3$ was decreased to 1.5 equiv, and DMPU was used as the solvent. Isolated yields and diastereoisomer ratios were determined after the conversion of the products to the poly-benzoylated compounds.

Scheme 1. Stereodivergent Propargylation of β-D-Lactose
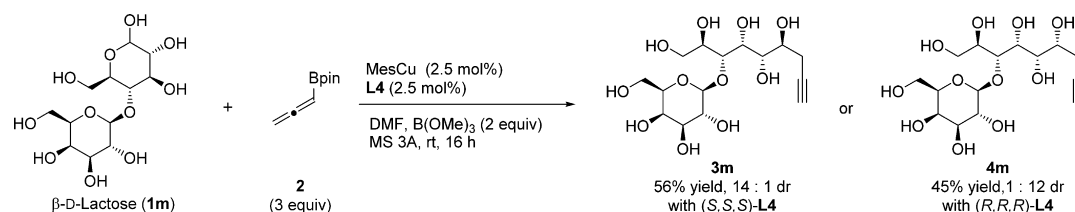
A was found to be suitable for *N*-acetyl-D-mannosamine (entries 19 and 20), while a slightly modified version of condition B (increased amount of Cu salt and using DMPU as the solvent) was effective for *N*-acetyl-D-galactosamine and *N*-acetyl-D-glucosamine (entries 21–24). Notably, the reaction with the disaccharide β-D-lactose (**1m**) proceeded smoothly under condition A to give **3m** and **4m** in good yield and excellent diastereoselectivity (Scheme 1).

Once the desired propargylation products were obtained, we tackled the synthesis of the corresponding sialic acid derivatives, starting by optimizing the synthesis of KDN from **3a**. The propargylation of D-mannose proceeded smoothly on a 1.8 g-scale using as little as 0.2 mol % of (*S*,*S*,*S*)-**L4**/MesCu. After quenching with MeOH, the mixture was concentrated. The crude solid was washed successively with EtOAc and MeOH to provide **3a** in 87% yield and >20:1 diastereoselectivity. With a sufficient amount of key intermediate **3a** in hand, we subsequently examined the chemoselective oxidation of the C−C triple bond to give an α-keto carboxylic acid group (Table 3). The consecutive 2-fold bromo-oxygenation of the C−C triple bond (one intramolecular and one intermolecular) proceeded effectively by a short (10 min) treatment of **3a** with Br₂ in aqueous solution to afford **5a**, which contains a pyranose skeleton. Subsequently, the dibromomethane moiety

was converted into the corresponding hydrate of the formyl group by hydrolysis under basic aqueous conditions (1 h). Finally, a short (10 min) Pinnick oxidation furnished the targeted natural KDN (**6a**) in 76% overall yield (Table 3). Following the same sequence, another relevant natural sialic acid, Neu5Ac (**6j**), and its unnatural C4-epimer (**6j′**) were synthesized from **3j** and **4j**, respectively. Since the propargylation proceeded with five-carbon aldoses, an unnatural eight-carbon analogue of sialic acid (**6d**) was also accessible starting from lyxose. The robustness of this synthetic strategy is illustrated by the conversion of **4m** into **6m**: unnatural disaccharide **6m**, containing a sialic acid residue at the reducing end, was also obtained in high yield using modified bromo-oxygenation conditions (KBr + oxone)[28] followed by hydrolysis and Pinnick oxidation.

■ **CONCLUSION**

In conclusion, we have developed a practical and short (four steps) synthetic route to various sialic acid derivatives, starting from readily available aldoses. The overall sequence does not require any protecting groups, and the oxidation states constantly increase.[29] Key to the success of this method is the copper-catalyzed stereodivergent propargylation, in which unprotected aldoses can be used. Even in the presence of a large excess of protic species and/or functional groups, the catalytically generated allenylcopper(I) species exhibits remarkable stability against protonolysis, still retaining high reactivity as a polar carbon nucleophile toward aldehydes. This unique characteristic is most likely due to the orthogonal reactivity between the soft allenylcopper(I) species and the hard hydroxy groups. Despite the complex chiral environments with multiple hydroxy groups present in the substrates, the diastereoselectivity of this process is controlled by the asymmetric catalyst. Subsequently, the propargylation products can be transformed into sialic acid derivatives via a simple three-step sequence. In addition, we successfully transformed the reducing end of a disaccharide into a sialic acid derivative selectively (from **4m** to **6m**); such reactivity should easily find applications in the artificial late-stage modification of sugar chains at the reducing end. The synthetic method reported herein offers general and straightforward access to a wide variety of sialic acid derivatives and thus promises potential applications in the context of drug discovery and investigations of biological functions.
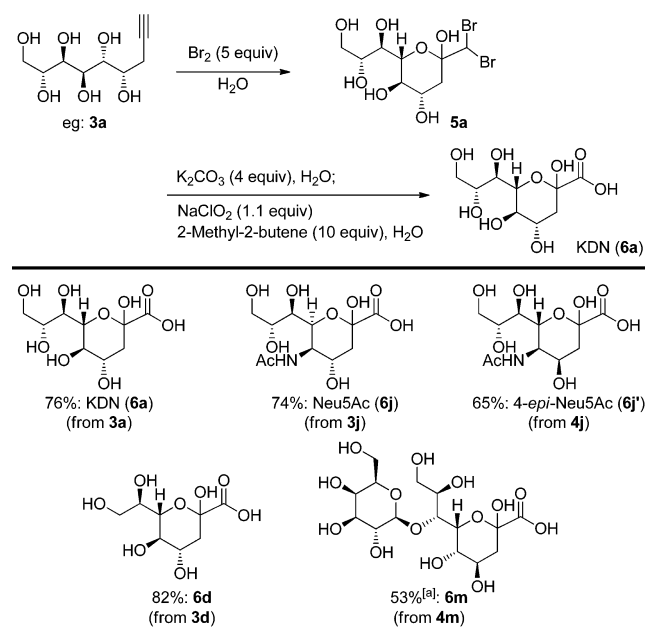
Table 3. Stereodivergent Synthesis of Sialic Acid Derivatives[a]

■ **ASSOCIATED CONTENT**

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.5b00360.

Experimental procedures and spectral data (PDF)

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Notes
The authors declare no competing financial interest.

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