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Catalytic Anomeric Aminoalkynylation of Unprotected Aldoses

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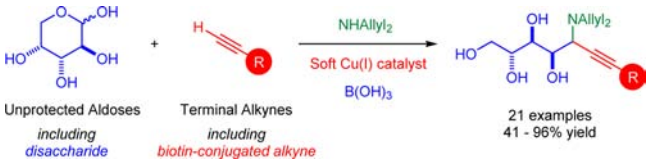
ABSTRACT



A copper(I)-catalyzed anomeric aminoalkynylation reaction of unprotected aldoses was realized. Use of an electron-deficient phosphine ligand, boric acid to stabilize the iminium intermediate, and a protic additive (IPA) to presumably enhance reversible carbohydrate−boron complexation were all essential for efficient conversion. The reaction proceeded well even with a natural disaccharide substrate, suggesting that the developed catalytic reaction could be useful for the synthesis of glycoconjugates with minimum use of protecting groups.

Oligosaccharides and glycoconjugates have significant roles in a diverse set of biological processes, such as viral infections, cell growth, and immunoresponses.[1] Synthesis of these highly polar, multifunctional molecules relies predominantly on the extensive use of protecting groups (PGs)[2] for chemo- and position-selective transformations.[3,4] The use of PGs, however, generally impairs synthetic efficiency[5,6] in terms of atom[7]- and step[8]-economy. These drawbacks of PGs are prevalent especially in the synthesis of carbohydrate derivatives. Although some studies have reported that a minimum use of PGs streamlines the synthesis of carbohydrate derivatives,[9] the number of such pioneering works is limited. These examples demonstrate that C−C bond-forming reactions at the anomeric carbon of unprotected carbohydrates are key components of the

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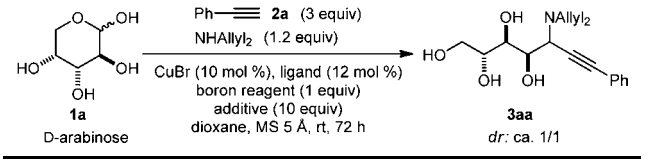
methodology. Representative nucleophiles applied in these reactions are the cyanide anion[10] (Kiliani reaction), nitromethane[11] (Fischer−Sowden reaction), phosphorus ylides,[12] 1,3-dicarbonyl compounds,[13] allyl metal species,[9a,14] vinyl boronic acid esters,[9b,c] and aryl compounds.[14h,15] Precedents that allow for the convergent incorporation of molecular skeletal fragments with multiple functional groups are scarce, however, despite their high synthetic utility. Furthermore, the available reports include only a limited number of catalytic reactions.[13j,l,m,14g,14h,15]

To broaden the scope of carbon nucleophiles that could be catalytically coupled with unprotected aldoses, we became interested in alkynes. Specifically, aminoalkynylation[16] of unprotected aldoses[17] affords nitrogen-containing polyol structures with elongated carbon chains[18] that could be potential synthetic intermediates for nitrogen-containing higher-carbon sugars.[19] In addition, the reaction would be useful for the concise synthesis of glycoconjugates of functional organic molecules, such as biotin derivatives and fluorescent probes. The orthogonal reactivity of soft nucleophile[20] and hard hydroxy groups of the substrate would be an essential factor to realize the target C−C bond formation. We herein report a copper-catalyzed anomeric aminoalkynylation reaction of unprotected aldoses.

Table 1. Optimization of Catalytic Aminoalkynylation of D-Arabinose



entry	boron reagent	ligand	additive	yield
1[a,b]	none	none	none	0%
2[a,b]	$BF_3 \cdot OEt_2$	none	none	18%
3	$PhB(OH)_2$	none	none	30%[c]
4	$B(OH)_3$	none	none	51%
5	$B(OEt)_3$	none	none	51%
6	$B(OH)_3$	PPh_3	none	50%[c]
7	$B(OH)_3$	xantphos[e]	none	47%[c,d]
8	$B(OH)_3$	dppe[f]	none	trace
9	$B(OH)_3$	$P(3,5\text{-}(CF_3)_2\text{-}C_6H_3)_3$	none	65%[c]
10	$B(OH)_3$	$P(C_6F_5)_3$	none	73%[c]
11	$B(OH)_3$	none	IPA	62%
12	$B(OH)_3$	$P(3,5\text{-}(CF_3)_2\text{-}C_6H_3)_3$	IPA	71%[c]
13	$B(OH)_3$	$P(C_6F_5)_3$	IPA	84%

[a] 30 mol % of CuBr and 3 equiv of diallylamine were used. [b] Reaction time was 12 h. [c] Determined by ^1H NMR [d] *dr*: 1.8/1 [e] xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethyl-xanthene [f] dppe: 1,2-Bis(diphenylphosphino)ethane.

We began our investigations using D-arabinose (**1a**), ethynylbenzene (**2a**), and several amines as substrates and Cu(I) salts as a catalyst. Initially, we tested CuBr and diallylamine by following Knochel's precedent,[21] but obtained no desired product (Table 1, entry 1). We hypothesized that the low reactivity of arabinose was due to its dominant hemiacetal form rather than a reactive aldehyde form.[22] We therefore used Lewis acid additives, expecting that they would promote the formation of the aldehyde form from the hemiacetal form of arabinose. Although the reactions with most Lewis acids were

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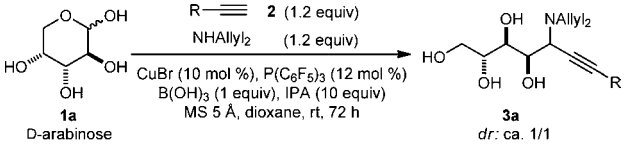
(22) No aldehyde form was observed in NMR analysis of arabinose in dioxane-d_8.

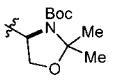
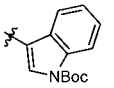
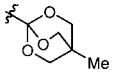
unsuccessful,[23] product **3aa** was obtained in 18% yield by the addition of 1 equiv of $BF_3 \cdot OEt_2$ (entry 2). Encouraged by this preliminary result, we further screened boron reagents and found that less acidic phenylboronic acid, boric acid, and triethylborate afforded higher product yields than $BF_3 \cdot OEt_2$ (entries 3 to 5). These results suggest that the boron reagents improved the yield, not by acting as a Lewis acid, but by forming boron acetals with arabinose.

Next, we investigated the effects of ligands for the copper atom. Use of standard phosphine ligands did not improve the reactivity (entries 6 and 7), and some of the bidentate phosphine ligands (entry 8) and nitrogen-based ligands significantly inhibited the reaction. On the other hand, electron-deficient tris(pentafluorophenyl)phosphine significantly improved the reactivity (entry 10).

Given that phenylboronic acid gave less satisfactory results than boric acid[24] and triethylborate (Table 1, entry 3 vs entries 4 and 5) despite its ability to form stable complexes with the diol moieties[25] of carbohydrates, we speculated that the reversible complexation between arabinose and boron reagents might be important for the higher reactivity.[26] Thus, we next examined alcohol additives

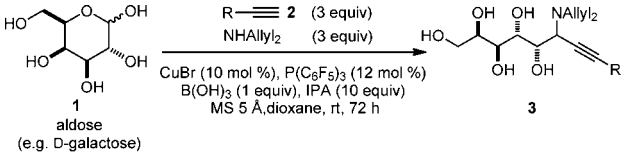
Table 2. Scope of Catalytic Aminoalkynylation Reaction for Alkyne Substrates

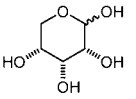
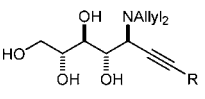
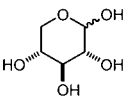
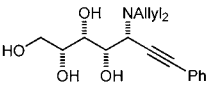
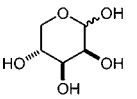
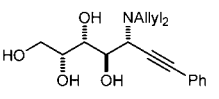
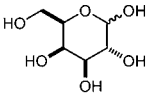
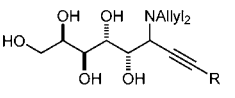
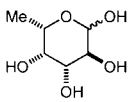
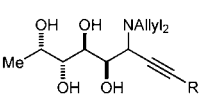


entry		product R	yield	entry		product R	yield
1[a]	**3aa**	Ph	84%	9	**3ai**		84%[b]
2[a]	**3ab**	TIPS	85%				
3	**3ac**	C_5H_{11}	79%				
4	**3ad**		76%	10	**3aj**		96%
5	**3ae**	CH_2OTBS	81%				
6	**3af**	CH_2OAc	72%				
7	**3ag**	CH_2NHBoc	81%				
8	**3ah**		78%	11	**3ak**		96%

[a] 3 equiv of alkyne were used. [b] *dr*: 1.9/1.

Table 3. Scope of Aminoalkynylation Reaction for Aldose Substrates



entry	aldose	product		yield *dr*
1	 D-ribose (**1b**)		**3ba** R = Ph	45% >20/1
2			**3bj** R = 	52% >15/1
3[a]	 D-xylose (**1c**)		**3ca**	41% 2.3/1
4	 D-lyxose (**1d**)		**3da**[b]	18% >10/1
5	 D-galactose (**1e**)		**3ea** R = Ph	50% 1/1
6			**3ee** R = CH_2OTBS	47% 1/1
7[a]	 L-fucose (**1f**)		**3fa** R = Ph	50% 1/1
8[a]			**3fg** R = CH_2NHBoc	64% 1/1
9[a]			**3fi** R = 	84% 1.9/1

[a] 1.2 equiv of diallylamine were used. [b] The stereochemistry of the major product is only speculative.

that would enhance the reversibility of the carbohydrate–boron complexation (Table 1, entries 11–13). The combined use of the electron-deficient phosphine ligand and IPA (10 equiv) led to product **3aa** in 84% yield (entry 13).[27,28] Diastereoselectivity, however, was not induced in most cases.

Having determined the optimal conditions, we tested the substrate scope. The scope of alkynes was examined using D-arabinose as an aldose substrate (Table 2). The reactivity was not markedly influenced by the substituents of alkynes, and in most cases the use of excess amounts of the alkyne was not necessary to achieve high conversion. Notably, alkynes with synthetically useful functional groups, such as a protected aminoalcohol moiety (entry 9), an indole ring

(23) We examined several Lewis acid additives, such as $Al(OTf)_3$, $Sn(OTf)_2$, $LiClO_4$, and $FeCl_3$, but no target product was obtained in any case.

(24) (a) Van Duin, M.; Peters, J. A.; Kieboom, A. P. G.; Van Bekkum, H. *Tetrahedron* **1985**, *41*, 3411. (b) van den Berg, R.; Peters, J. A.; van Bekkum, H. *Carbohydr. Res.* **1994**, *253*, 1. (c) Smith, B. M.; Owens, J. L.; Bowman, C. N.; Todd, P. *Carbohydr. Res.* **1998**, *308*, 173. (d) Furneaux, R. H.; Rendle, P. M.; Sims, I. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2011. (e) Ricardo, A.; Carrigan, M. A.; Olcott, A. N.; Benner, S. A. *Science* **2004**, *303*, 196. (f) Sponer, J. E.; Sumpter, B. G.; Leszczynski, J.; Sponer, J.; Fuentes-Cabrera, M. *Chem.—Eur. J.* **2008**, *14*, 9990.

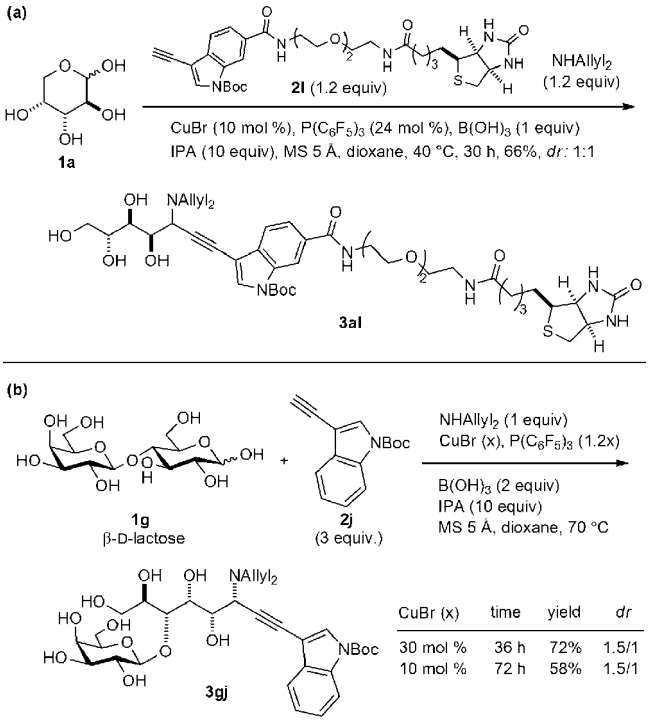
(25) For some representative reviews and articles on the complexation of carbohydrate and phenylboronic acid or its derivatives, see: (a) Duggan, P. J.; Tyndall, E. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1325. (b) Springsteen, G.; Wang, B. *Tetrahedron* **2002**, *58*, 5291. (c) Bérubé, M.; Dowlut, M.; Hall, D. G. *J. Org. Chem.* **2008**, *73*, 6471.

(26) Our hypothesis is that the desired aminoalkynylation would proceed from appropriate carbohydrate–boron complexes. Reversible carbohydrate–boron complexation might be necessary to access such reactive structures.

(27) Preliminary mechanistic studies and a tentative reaction mechanism are explained in the Supporting Information (SI) (sections 6–8).

(28) Control experiments suggested that boric acid does not simply work as a transient protecting group to free hydroxy groups in unprotected aldoses (see the SI, section 6).

Scheme 1. Catalytic Aminoalkynylation with Elaborated Substrates: (a) Reaction with Biotinylated Alkyne, (b) Reaction with Disaccharide



CuBr (x)	time	yield	dr
30 mol %	36 h	72%	1.5/1
10 mol %	72 h	58%	1.5/1

(entry 10), and a ketoester equivalent (entry 11), were competent without any loss of reactivity.

The scope of aldoses was also studied (Table 3). Among the other three aldopentoses, the reactions with ribose (entries 1 and 2) and xylose (entry 3) gave the target compounds in 40−50% yield, while the reaction with lyxose afforded the product in low yield (entry 4).[29] Intriguingly, high diastereoselectivity was observed in the reactions with ribose and lyxose, both of which have a *cis* 2,3-diol structure.[30] As for aldohexoses, galactose (entries 5 and 6) and fucose (entries 7 to 9) gave the products in greater than 40% yield.[31] These results suggest that the relative stereochemistry of aldoses is a crucial factor for the reactivity and diastereoselectivity.

We also examined the applicability of the developed method to the reaction using more elaborate substrates (Scheme 1). Alkyne **2l** linked to a biotin molecule was successfully used as a nucleophile in the reaction with arabinose (**1a**) to afford a biotin-conjugated[32] polyol **3al** in 66% yield (Scheme 1 a). The reaction with β-D-lactose as a representative disaccharide substrate was also attempted. Although the optimal conditions for monosaccharides afforded the product in only low yield, modification of the conditions in terms of the reaction temperature (70 °C) and amount of boric acid (2 equiv) successfully improved the yield. The use of 30 mol % CuBr afforded disaccharide-conjugated product **3fj** in 72% yield in 36 h (Scheme 1 b). The catalyst loading could be reduced to 10 mol % without a significant loss of reactivity (58%) if the reaction time was extended (72 h; Scheme 1 b). Specifically, the reaction proceeded selectively at the reducing terminal of the disaccharide. The tolerance to multiple free hydroxy groups and biologically significant functional groups suggests that the developed reaction could be a potential lead method for the concise synthesis of glycol-conjugates from sugars with reducing terminals.

In summary, we have developed a copper(I)-catalyzed aminoalkynylation reaction of unprotected aldoses. This convergent reaction can introduce molecular fragments, including a biotinylated alkyne, to the reducing terminal of natural carbohydrates. The catalytically generated nucleophile, copper alkynide, was tolerant to multiple hydroxy groups of the substrates and protic additives (boric acid and IPA), yet exhibited high nucleophilicity for the desired C−C bond formation. Boric acid was an essential additive, and the stereochemistry of the aldoses markedly influenced the reactivity, suggesting that the complexation modes of boric acid and aldoses are crucially related to the reaction process. Elucidation of the detailed complexation modes between boric acid and aldoses,[27] improvement of the diastereoselectivity with a wider range of aldose substrates, and extension of this catalytic method to drug lead synthesis with minimal use of protecting groups are ongoing.

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Supporting Information Available. Experimental procedures, syntheses and characterization of all new products, results of control experiments and preliminary mechanistic studies, and tentaive reaction mechanism. This material is available free of charge via the Internet at http://pubs.acs.org.

(29) Neither heating nor increasing the equivalents of boric acid improved the reactivity.

(30) A possible mechanism for the diastereoselective induction is explained in the SI.

(31) Reactions with typical aldohexsoses, such as D-glucose and D-mannose, afforded the products in very low yields.

(32) For a recent review on biotinylation of bioactive molecules, see: Trippier, P. C. *ChemMedChem* **2013**, *8*, 190.

The authors declare no competing financial interest.