論文の内容の要旨

論文題目　Development of Functional Group Tolerated Cu(I)-Catalyzed Asymmetric C-C Bond Forming Reactions

(保護基フリー合成を指向した不斉銅触媒による
C-C 結合形成反応の開発)

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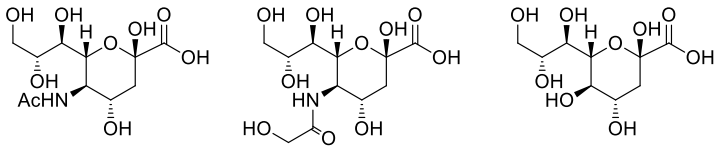
Research Background

Protecting groups have been widely used in synthetic organic chemistry. Despite the merits for secured molecular conversion, the atom- and step-economy of the overall molecular synthesis decreases. Thus, minimizing the use of protecting groups is critically important[1] toward realizing efficient molecular synthesis. Although nucleophilic addition of organometallic reagents to carbonyl compounds has played a pivotal role in organic synthesis since the original work of Butlerov[2a] and Grignard,[2b] such transformation are facing formidable challenge in the presence of unprotected protic functional groups. Since 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. My research involves the development of facile, catalytic reactions which were inert to protic functional groups and the application of the developed methodologies to the straightforward construction of complex molecules.

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

Sialic acids, which comprise a polyfunctionalized 9-carbon α-keto carboxylic acid skeleton (**Figure 1**), represent one of the most important constituents of glycoconjugates in biological system. Thus, rapid and scalable supply and broadening the structural diversity of sialic acids are an urgent demand in the current glycochemistry and glycobiology. Despite significant improvements in synthetic efficiency during past decades, there are still several points to be overcome: limited scope, unsatisfactory yield and scalability. Moreover, the flexibility in structural and stereochemical alternations is limited.

Figure 1. Representative Sialic Acid

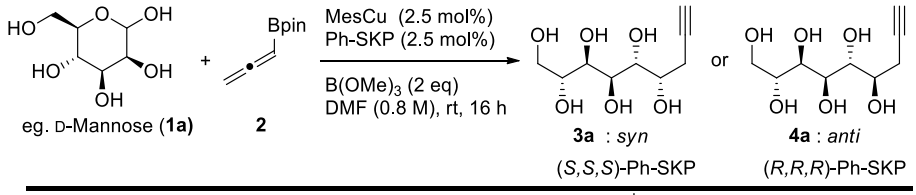


To overcome the limitation, I envisaged that the use of an asymmetric copper catalyst would be capable of controlling the stereochemistry of the C–C bond-formation at the anomeric carbon of unprotected aldoses. To be specific, I focused on the development of catalyst-directed stereodivergent propargylation of unprotected aldoses.[3]

The initial screening of reaction conditions identified that $B(OMe)_3$ was essential to improve reactivity by accelerating the ring-opening process of cyclic hemiacetal form of aldoses and increasing the concentration of the reactive aldehyde. The diastereoselectivity of the key propargylation step could be completely controlled by using a chiral ligand (Ph-SKP) and the stereoselectivity was simply switched by changing the absolute configuration of the chiral copper catalyst. Under the optimized conditions, substrate generality was investigated (**Table 1**). Using ligands with 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-(**1c**) and six-carbon aldoses (**1a**, **1b** and **1d**). A modified version using $CuClO_4(MeCN)_4$ and CF_3COOK combination was suitable for 2-deoxy type aldoses (**1e**). Notably, the reaction with β-D-lactose (**1f**) proceeded smoothly to give the corresponding target molecules **3f** and **4f** in good yield and excellent diastereoselectivity. The outstanding stereo-control ability and the tolerance to multiple free hydroxy groups made the developed reaction a general method for the concise synthesis of polyol-containing terminal alkyne modules.

The obtained products could be converted to sialic acid derivatives through simple

Table 1. Substrate Scope of the Stereodivergent Propargylation of Unprotected Aldoses.[a]

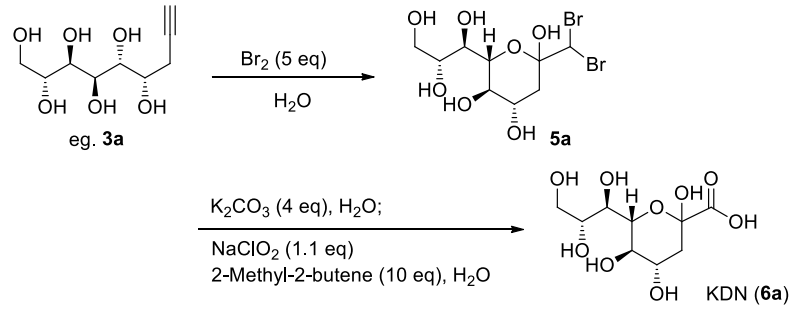


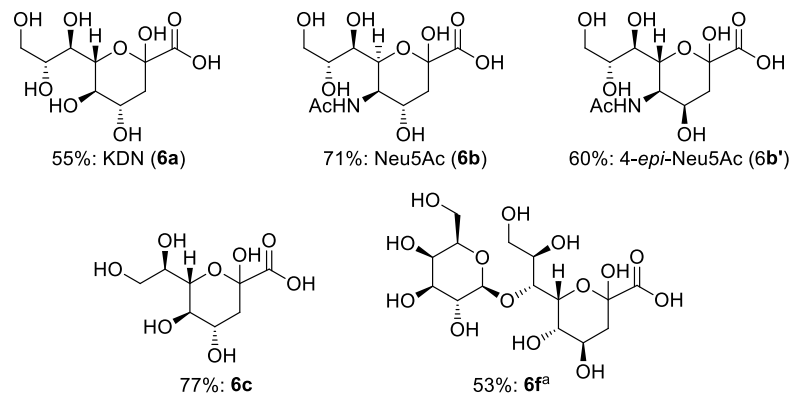
	D-Mannose (**1a**)	N-Acetyl-D-Mannosamine (**1b**)[b]	D-Lyxose (**1c**)
Ligand			
S	**3a**: 90%, >20:1	**3b**: 70%, >20:1	**3c**: 84%, >20:1
R	**4a**: 81%, 1:>20	**4b**: 51%, 1:>20	**4c**: 81%, 1:>20

	D-Glucose (**1d**)[b]	2-Deoxy-D-Glucose (**1e**)[b,c]	β-D-Lactose (**1f**)[b]
Ligand			
S	**3d**: 76%, >20:1	**3e**: 59%, >20:1	**3f**: 56%, 14:1
R	**4d**: 72%, 1:3.5	**4e**: 52%, 1:17	**4f**: 45%, 1:12

[a]Isolated yield. Diastereomeric ratio was determined by ^1H NMR analysis of the crude mixture.
[b]Molecular sieves (MS 3A) was used. [c]$CuClO_4(MeCN)_4$ (2.5 mol%), CF_3COOK (5 mol%).

Table 2. Stereodivergent Synthesis of Sialic Acid Derivatives





[a] KBr and oxone were used instead of Br_2 for bromo-oxygenation.

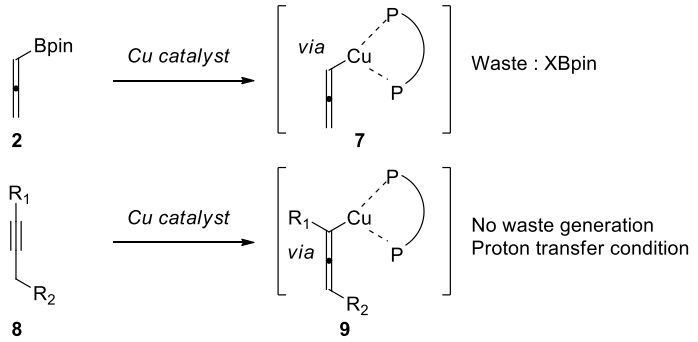
three-step sequence. The consecutive 2-fold bromo-oxygenation of the C-C triple bond (one intramolecular and one intermolecular) proceeded effectively by a short (10 min) treatment of **3a** with Br_2 in aqueous solution to afford **5a**, which contains a pyranose skeleton. Subsequently, the dibromomethane moiety was converted into the corresponding hydrate of the formyl group by hydrolysis under basic aqueous conditions. Finally, a short Pinnick oxidation furnished the targeted natural KDN (**6a**) in 76% overall yield (**Table 2**). Following the same sequence, another relevant natural sialic acid, Neu5Ac (**6b**), and its unnatural C4-epimer (**6b'**) were synthesized from **3b** and **4b**, respectively. Since the propargylation proceeded with five-carbon aldoses, an unnatural eight-carbon analogue of sialic acid (**6c**) was also accessible starting from lyxose. The robustness of this synthetic method is further illustrated by the conversion of **4f** into **6f** using modified bromo-oxygenation conditions.

In conclusion, a catalytic stereodivergent propargylation of unprotected aldoses was developed. The diastereoselectivity was completely controlled by catalyst system even in the presence of complex chiral environment with multiple hydroxy groups. The propargylation products could be transformed to sialic acid derivatives by following simple three-step sequence. This synthetic method offers general and straightforward access to the synthesis of various sialic acid derivatives which can be a useful tool for further biological function elucidation.

2. Ligand-Controlled Copper(I)-Catalyzed Regiodivergent Synthesis of Conjugated and Skipped Ene-ynes

Although anomeric propargylation was achieved using aldoses in the absence of protecting groups, the methodology developed still required pre-activated reagents **2** (**Figure 2**), and the stoichiometric waste (XBPin), generated during the reaction, hampered the overall efficiency. To overcome the limitation and further expand the application scope, novel strategy to generate allenyl-copper intermediate **9** *via* hydrogen transfer process will be of great importance.

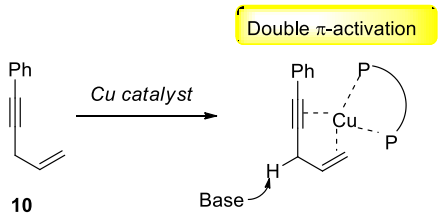
Figure 2. Working Hypothesis.



Taking advantage of copper(I) Brønsted base catalysts, a series of asymmetric reactions have been developed.[4] In all cases, electron-withdrawing group was required for the coordination with catalyst and acceleration of the deprotonation process. Direct catalytic deprotonation via π-activation in the absence of hetero-atom remains unexplored.

Our working hypothesis is shown in **Figure 3**. We expect the copper catalyst enable the deprotonation process via the novel "double π-activation". Following this concept, readily available skipped ene-yne **10** (**Figure 4**) as substrate, the nucleophilic addition proceeded successfully in the presence of unprotected hydroxy group of cyclic hemiaminal (**11**).[5] The use of (*S*)-DTBM-SEGPHOS furnished the terminal adduct **13** in high yield with excellent regioselectivity and *cis/trans*

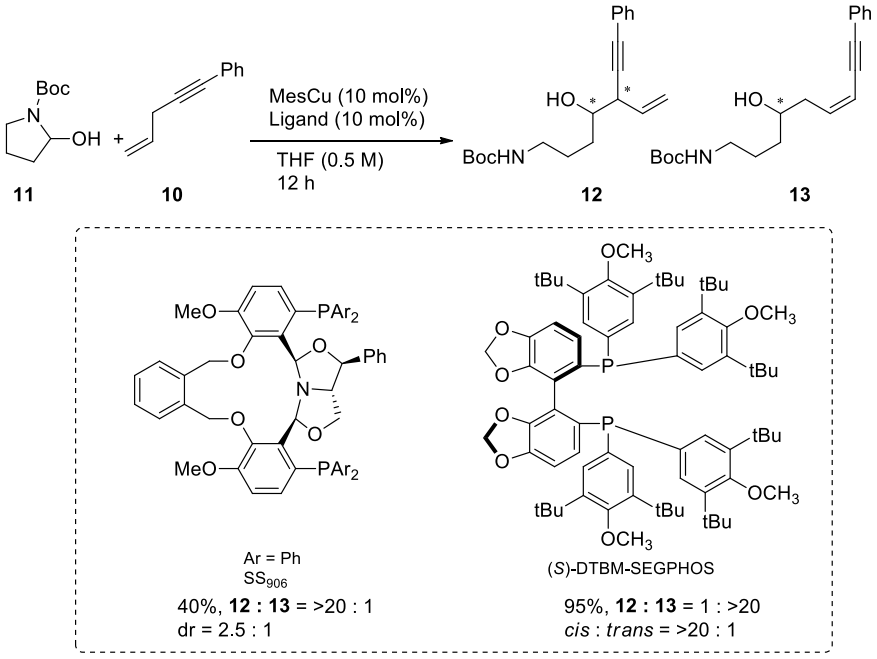
Figure 3. Reaction Design



selectivity, while using SS_{906} predominantly afforded the internal adduct **12**.

In summary, a catalytic regiodivergent synthesis of conjugated and skipped ene-ynes was developed. Ligand effect was predominant for the regio-control in the addition step. Currently, further investigation toward improving the reactivity for the internal addition is on-going.

Figure 4 . Ligand-Controlled, Regiodivergent Nucleophilic Addition



References

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