論文の内容の要旨

論文題目　Catalytic Asymmetric Iterative Aldol Reaction
for the Rapid Synthesis of 1,3-Polyols
(触媒的不斉多連続アルドール反応によるポリオール合成)

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Introduction

1,3-Polyols are ubiquitous structural motifs in biologically active polyketide natural products and drugs.[1] For accessing these motifs, cross-aldol reaction between two different aldehydes would be a powerful synthetic method, providing an aldehyde moiety for the subsequent iterative aldol reactions (Figure 1A, upper row).[2]

Although the idea of iterative cross-aldol reactions of aldehydes is conceptually simple, even a simple aldehyde-aldehyde cross aldol reaction[3] is known to be challenging because of the donor/acceptor control and instability of the product (Figure 1A, bottom row). Furthermore, the number of possible isomers increases exponentially as the multi-aldol reaction proceeds, and the products exist as a cyclized hemiacetal form lacking the reactive aldehyde moiety. Precedent examples are only limited to catalytic asymmetric double-aldol reactions[4] and a catalytic diastereoselective triple-aldol reaction[5]. There is much room left especially with regard to the substrate generality and practicality.

The strategy to achieve the goal is shown in Figure 1B. The selective generation of chiral and reactive copper(I) enolate would be realized through isomerization of allyl alcohol derivatives, followed by transmetalation from boron to copper. After aldol additions, copper aldolates are trapped by
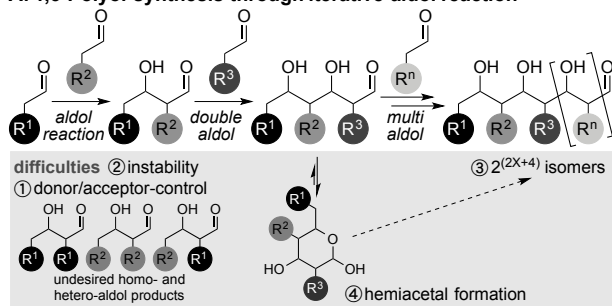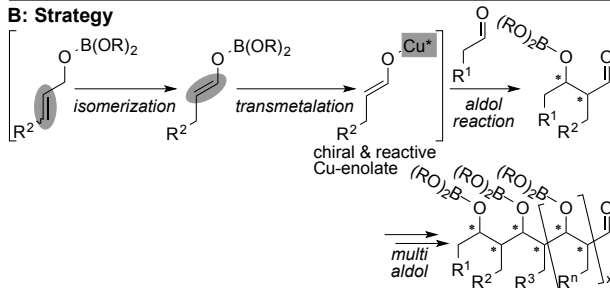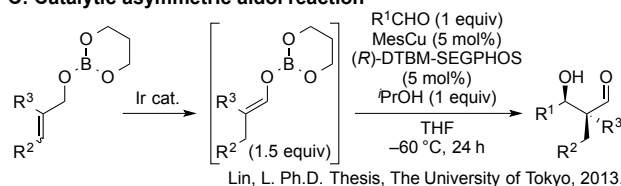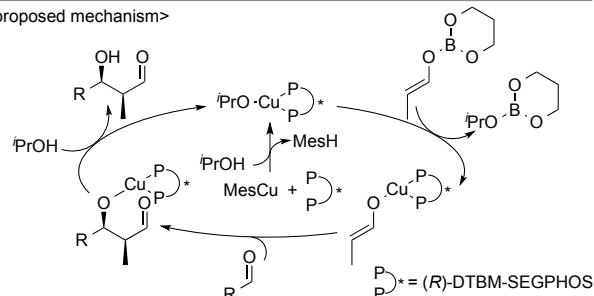

Figure 1. (A) An ideal approach to 1,3-polyols through aldol reaction (upper row) and its potential difficulties (bottom row). (B) A strategy for the catalytic asymmetric iterative aldehyde cross-aldol reaction. (C) The previous achievement in the Kanai group (upper row) and its plausible catalytic cycle (bottom row).

boron, generating *O*-protected aldol products and thus preventing the formation of unreactive hemiacetal in more than double-aldol reactions.

Based on this strategy, Dr. Lin, previously in the Kanai group, found that the MesCu/DTBM-segphos catalysis generates chiral β-hydroxy aldehydes in good yields and stereoselectivity (Figure 1C, upper row).[6] The plausible catalytic cycle is depicted in Figure 1C, bottom row. By mixing MesCu, chiral ligand, and isopropanol, chiral CuO^{i}Pr is generated with the extrusion of mesitylene. Transmetalation between the copper alkoxide and boron enolate affords chiral copper enolate, which reacts with acceptor aldehyde to form copper aldolate.[7] Facile protonation of this intermediate forms the product and regenerates the catalyst.

Results & Discussion

To extend this approach to the double-aldol reaction, there were two major tasks; reactivity and analytical method. Although the copper catalysis realized the single-aldol reaction, the reactivity was not sufficient for the double-aldol reaction (Table 1, entry 1). To increase the reactivity, the diol moiety of boron enolates was evaluated, anticipating that both the increased electron density and the Thorpe-Ingold effect would enhance the efficiency of the transmetalation step (Table 1, entries 2−8). As expected, pinacol containing boron enolate

**Table 1. Evaluation of the diol moiety of boron enolates**

entry	ξ−B(OR)$_2$	single:double:triple*	dr of double-aldol products* (**A1**:**B1**:other isomers)
1	ξ-B(O-O)	79 : 17 : 4	79 : 6 : 15
2	ξ-B(O-O)	88 : 10 : 2	100 : 0 : 0
3	ξ-B(O-O)	100 : 0 : 0	ND
4	ξ-B(O-O)	99 : 1 : 0	ND
5	ξ-B(O-O)	**38 : 62 : 0**	**96 : 2 : 2**
6	ξ-B(O-O)	100 : 0 : 0	ND
7	ξ-B(O-O)	ND†	ND
8	ξ-B(O-O)	100 : 0 : 0	ND

*The ratio of single-/double-/triple-aldol products and diastereoselectivity were determined based on the area% of LC/MS chart. †Aldol products were not observed. ND = not determined.

Table 2. Evaluation of additives

entry	additive (x mol%)	single:double:triple:quadruple*	dr†
1	^{i}PrOH (5)	26 : 70 : 3 : 1	92 : 4 : 4
2	^{i}PrOH (100)	38 : 62 : 0 : 0	96 : 2 : 2
3	**4-MeO-C$_6$H$_4$OH (100)**	**1 : 97 : 2 : 0.1**	**96 : 1 : 3**
4	^{i}PrOH (5) + Et$_3$N (5)	1 : 67 : 28 : 4	96 : 2 : 2
5‡	^{i}PrOH (5) + Et$_3$N (200)	6 : 8 : 83 : 3	65 : 14 : 21
6	^{i}PrOH (100) + Et$_3$N (200)	2 : 49 : 47 : 2	94 : 2 : 4

*The ratio of single-/double-/triple-/quadruple-aldol products were determined based on the area% of LC/MS chart. †Diastereomeric ratio refers to the ratio of **A1**:**B1**:other isomers. ‡Mitsunuma, H. Ph.D. Thesis, The University of Tokyo, 2015.
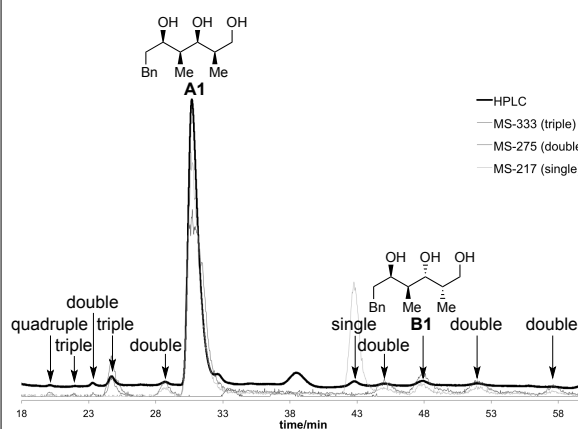
Figure 2. LC/MS chart of the crude reaction mixture of Table 2, entry 3. The thick line is HPLC spectrum and the thin lines are MS spectra of single-aldol products [M+Na]$^+$, double-aldol products [M+Na]$^+$, and triple-aldol products [M+Na]$^+$.

enhanced the reactivity to generate double-aldol product as a major product (Table 1, entry 5). To further increase the efficiency by facilitating the protonation of the copper aldolate intermediate, protic additives were evaluated (Table 2). As in entry 3, relatively acidic 4-methoxyphenol instead of isopropanol gave high yield and diastereoselectivity. The ratio of single-/double-/triple-/quadruple-aldol products and diastereoselectivity were evaluated after reduction with LiBH$_4$. Thus obtained crude reaction mixture was analyzed by LC/MS using Daicel iCHIRAL-6 (Figure 2).

Under optimized conditions, substrate generality was investigated (Table 3). As acceptors, not only aliphatic but also α,β-unsaturated and aryl aldehydes could be utilized to generate the desired triols **A** in good yield and stereoselectivity (entries 1–4). Stepwise introduction of different donors at the first and second steps was also possible using single-aldol products as acceptor aldehydes (entries 5 and 6). Furthermore, switching the chirality of the catalyst in the first and second aldol reactions provided stereodivergent access to triols **B** (entries 7−10). Both the enantioselectivity and diastereoselectivity were predominantly controlled by the catalyst, not by the substrates.

Table 3. Copper-catalyzed asymmetric double-aldol reaction

entry	acceptor	donor	product	yield (%) dr* ee (%)
<with (R)-DTBM-SEGPHOS>				
1	Bn	Me	Bn Me Me	86% yield 96:1:3 dr >99% ee
2	Bn	Et	Bn Et Et	85% yield 98:0:2 dr >99% ee
3†	Ph	Me	Ph Me Me	89% yield 86:14 dr >99% ee
4†,‡	Ph	Et	Ph Et Et	58% yield 94:6 dr >99% ee
5	Bn Me	Et	Bn Me Et	72% yield 92:4:4 dr >99% ee
6	Bn Et	Me	Bn Et Me	93% yield 92:1:7 dr >99% ee

entry	acceptor	donor	product	yield (%) dr* ee (%)
<with (S)-DTBM-SEGPHOS>				
7	Bn Me	Me	Bn Me Me	61% yield 4:92:4 dr >99% ee
8	Bn Et	Et	Bn Et Et	63% yield 2:95:3 dr >99% ee
9	Bn Me	Et	Bn Me Et	64% yield 4:94:2 dr >99% ee
10	Bn Et	Me	Bn Et Me	71% yield 6:80:14 dr >99% ee

The diastereomeric ratio was determined by LC/MS analysis of the crude reaction mixture. Enantiomeric excess was determined by HPLC. Yield refers to the combined yield of all diastereomers. *Diastereoselectivity refers to the ratio of **A:B**:other isomers. †Diastereoselectivity refers to the ratio of **A**:minor diastereomers. ‡2 equiv of triethylamine was added.

Conclusion

The stepwise switching of the donors and stereoselectivity in the first and second steps of the iterative double-aldol reaction was achieved. Together with the single-aldol reaction developed by Dr. Lin[6] and triple- and quadruple-aldol reactions found by Dr. Mitsunuma,[8] these findings demonstrate that the copper-catalyzed asymmetric iterative cross-aldol reactions of aldehydes could serve as an ideal method for 1,3-polyol synthesis.

References

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